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Good, better or best: A study of standards of prevention and care in HIV prevention trials

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Supervisor's Certification

I, Dr Christopher Jordens, certify that the PhD thesis entitled 'Good, better or best: A study of standards of prevention and care in HIV prevention trials' by Bridget Haire is in a suitable form for examination.

…….

Christopher Jordens

…….

Date

Candidate's Declaration

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Abstract

Introduction

This is a study of the negotiation of benefits in HIV biomedical prevention trials. It took place at a very dynamic period in HIV prevention research, 2009-2012, during which there were positive efficacy results from six large, randomised controlled trials of HIV prevention interventions.

This study presents evidence on how benefits to participants are negotiated in efficacy trials of biomedical HIV prevention technologies. It re-considers debates about obligations to trial participants in the light of the positive trial results and asks how partially effective HIV prevention modalities impact on these debates.

Methods

Empirical

The empirical components of the study comprise:

- a survey of principal investigators who conducted HIV prevention trials
- 14 in-depth interviews with principal investigators; and
- additional data collection from document analysis and personal communications.

Descriptive statistics were calculated for survey responses, and interview data were analysed thematically from a symbolic interactionist perspective.

Normative

The normative component focuses on four big-picture issues:

- Whether there is ethical justification for antiretroviral (ARV)-based prevention in HIV endemic areas;
- How the positive HIV prevention trial results – which demonstrate *partial* efficacy – affect (or should affect) future HIV prevention research;
- The implications of incorporating newly validated technologies into the standard of prevention; and
- Whether PrEP should become the comparator arm in HIV prevention trials from now on.

Results

Procedural norms have developed regarding some aspects of standard of prevention. There are differences however regarding whether standards of prevention should be basic or optimal, and whether or when new interventions should be added.

Access to ARV for seroconverters, usually through partnerships, has also become a norm, and some principal investigators also reported a strong obligation towards those 'screened out' of trials – volunteers with pre-existing HIV infection. The importance of various forms of ancillary care provision was recognised and negotiation of this care helped establish the research project as part of a healthcare continuum.

Post-trial access provisions were in place for all the interventions that had successful efficacy results. There were significant differences in both the duration and the timeliness of actual post-trial provision, however.

Conclusion

Partially effective interventions pose problems for enduring post-trial access as by definition, they raise questions about ‘how good is good enough’ for implementation within particular epidemic settings. A similar dilemma is faced with regard to standard of prevention. The key question facing HIV prevention research is how to test new experimental interventions in the context of partially effective interventions. Ongoing research into new intervention is crucial, but reducing HIV incidence in trial populations is a legitimate goal. Hence, it is time to include a proven biologically effective intervention as an active comparator in HIV prevention trials. The goals of HIV prevention research must be to find the most effective ways of using existing tools and to establish the effectiveness of new tools. An active comparator balances the need to protect participants with the need to develop new interventions.

For Marion and Lucy, whose manifold perfections inspire me ever to strive.

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Professor John Kaldor had no formal supervisory role in this research, but his gregarious collegiality led to him playing a significant role in many aspects. John persuaded several elusive principal investigators to talk to me. He also (rightly) insisted on my principal investigator survey being redesigned, provided a sounding board for many of the key ideas in this thesis, and acted as a co-author on two articles. I am immensely grateful for his input.

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List of publications and presentations

Peer reviewed articles included in this thesis

Haire B., and C. Jordens. 2013. Standard of prevention in the real world: A qualitative study of principal investigators in HIV biomedical prevention trials. *AJOB Primary Research.* Accepted Feb 26, 2013

Haire B., and J. Kaldor. 2013. Ethics of ARV-based prevention: PrEP and treatment-as-prevention. *Developing World Bioethics*. Accepted Jan 10, 2013.

Haire, **B.,** M. Folayan, C. Hankins, J. Sugarman, S. McCormack, G. Ramjee and M. Warren. 2013. Ethical considerations in determining standard of prevention packages for HIV prevention trials: Examining PrEP. *Developing World Bioethics*. Accepted Jan 10, 2013.

Haire, B. 2013. Ethics of medical care and clinical research. *Journal of Medical Ethics*. 2013;**39:**231-235. Published Online First: 22 November 2012 doi:10.1136/medethics-2012-100936

Haire, B. J. Kaldor, C.F.C. Jordens. 2012. How good is 'good enough': When should new HIV technologies should become standard of care? *American Journal of Bioethics* 2012, 12(6):21-30.

Haire, B. 2011. Because we can: Clashes of perspective over obligation in the failed PrEP trials. *Developing World Bioethics*, 11 (2):63-74.| DOI: 10.1111/j.1471-8847.2010.00292.x

Relevant peer-reviewed articles not included in this thesis (available in Appendix C)

McGregor, S., G. Tachedjian, B.G. **Haire**, J.M. Kaldor. 2013.The Seventh and last international microbicides conference: From discovery to delivery. *Sexual Health.* Accepted January 16, 2013.

Haire, B. 2011.Treatment-as-prevention needs to be considered in the just allocation of HIV drugs. *American Journal of Bioethics* 11(12):48-50

Haire, B. 2009. Back to basics in clinical research ethics. *American Journal of Bioethics*, 9:3, 48-49.

Oral presentations

Haire, B. 2012. Ethics of ARV-based prevention. Paper 420. Australasian Society of HIV Medicine Conference. Melbourne, Australia; October 2012.

Haire, B. 2012. Standard of Prevention: A qualitative study of Principal Investigators' perspectives. Microbicides 2012 Conference. Sydney, Australia; April 2012. Available at: https://secure.ashm.org.au/ei/viewpdf.esp?id=82&file=c%3A%5CCertain%5CEventwin%5Cdocs%5Cpdf%5Cc12micAbstract00619%2Epdf

Haire, B., J. Kaldor. 2011. Designing ethical HIV prevention trials. Australasian Society of HIV Medicine Conference. Canberra, Australia; October 2011. Available at: https://secure.ashm.org.au/ei/viewpdf.esp?id=81&file=c%3A%5CCertain%5CEventwin%5Cdocs%5Cpdf%5Cc11asAbstract00527%2Epdf

Haire, B. 2011. How good is 'good enough'? Determining when new HIV prevention technology should become standard of care. 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention Conference. Rome, Italy; July 2011.

Haire, B., J. Kaldor. 2010. Power vs Prevention: Trading standards in prevention trials. Paper 533. Australasian Society of HIV Medicine Conference. Sydney, Australia; October 2010. Available at http://www.hivaidsconference.com.au/images/UploadedFiles/HIVAIDS2010-Handbook_TEXT.pdf

Haire, B. Ethical issues in microbicide research. Microbicides 2010 Conference. Pittsburgh, USA; May 2010.

Haire, B. 2010.Standards of care in HIV biomedical prevention trials in the developing world: a comparison. Evolving Knowledge and Practice: 11th Social Research Conference on HIV, Hepatitis C and Related Conditions. Sydney, Australia; April 2010.

Invited speaker presentations

Haire, B. 2012. Ethics in a New Era – plenary. Microbicides pre-conference. Sydney, Australia; April 2012. Available at: http://www.rectalmicrobicides.org/docs/m2012presos/ethics_new_eraM2012.ppt

Haire, B. 2012. Perspectives on new HIV prevention technologies Silence&articulation, the 12th Social Research Conference on HIV, Hepatitis and Related Diseases (HHARD). Sydney, Australia, April 2012.

Haire, B. 2011. Test and Treat Debate – evaluable, applicable and relevant in our region or just plain crazy? Australasian Society of HIV Medicine Conference. Sydney, Australia; October 2010.

Haire, B. 2009. PrEP: is it viable? Conference debate. Australasian Society of HIV Medicine/Sexual Health Conference. Brisbane, Australia; September 2009.

Acronyms and abbreviations

ACON	AIDS Council of New South Wales
AIDS	Acquired immune deficiency syndrome
ALVAC	Brand name of Sanofi Pasteur vaccine
ART	antiretroviral therapy
ARV	antiretroviral (drug)
AVAC	AIDS Vaccine Advocacy Coalition
AZT	Zidovudine, ZDV. An antiretroviral drug
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CAPRISA 004	Phase IIb study of tenofovir gel as a vaginal microbicide
CDBI	Council of Europe's Steering Committee on Bioethics
CDC	Centers for Disease Control (US)
CIOMS	Council for International Organizations of Medical Sciences
COL 1492	Microbicide trial that tested nonoynol-9
CONRAD	Contraception Research and Development
DSMB	Data Safety Monitoring Board
EGE	European Group on Ethics in Science and New Technologies
FDA	Food and Drug Administration (US)
FEM-PrEP	Pre-exposure Prophylaxis Trial for HIV Prevention among African Women
FTC	Emtricitabine, an antiretroviral drug
GCM	Global Campaign for Microbicides
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network

HTPN 052	Prevention trial that tested ‘treatment as prevention’
IAVI	International AIDS Vaccine Initiative
ICH-GCP	International Conference on Harmonisation Good Clinical Practice Guidelines
iPrEx	Preexposure Prophylaxis Initiative. Trial of PrEP in men who have sex with men.
IRB	Institutional Review Board
IRMA	International Rectal Microbicides Advocates
MCC	Medicines Control Council (South Africa)
MDP 301	Prevention trial that tested vaginal microbicide Pro 2000
MIRA	Methods for Improving Reproductive Health in Africa – trial of diaphragm for HIV prevention
MRC	Medical Research Council
MTN	Microbicides Trial Network
N-9	nonoxnol-9, agent tested as a microbicide
NBAC	National Bioethics Advisory Commission (US)
NIH	National Institutes of Health (US)
PACTG076	(Prevention AIDS Clinical Trial Group). Trial of AZT to prevent mother-to-child transmission.
PrEP	Pre-exposure prophylaxis (preventive treatment before exposure to reduce the risk of HIV acquisition).
Pro 2000	Agent tested as a vaginal microbicide
RCT	randomised control trial
Rgp120	Agent tested as a vaccine. Also called AIDSVAX.
RV 144	Vaccine trial held in Thailand that tested a combination prime and boost vaccine strategy

SMART	Strategies for Management of Antiretroviral Therapy study
START	Strategic Timing of Anti-Retroviral Treatment study
STEP	(Not acronym) Test-of-concept vaccine trial. Also called HVTN 502.
STI	sexually transmissible infections
TasP	Treatment-as-prevention
TDF	Tenofovir disoproxil fumarate, an antiretroviral drug. Always shorted to 'tenofovir' in this thesis
TDF-2	Trial of combined oral PrEP in heterosexual people in Bostwana.
UK	United Kingdom
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNESCO	United Nations' Educational, Scientific and Cultural Organisation
US	United States
VAXGen	Company that produced the first HIV vaccine candidate.
VOICE	Vaginal and Oral Interventions to Control the Epidemic. Trial of oral PrEP, combined oral PrEP and tenofovir gel.
WHO	World Health Organization
WMA	World Medical Association

Names of drugs, prevention trials and prevention agents[1]

Antiretroviral drugs

AZT	Also known as zidovudine or ZDV. The first antiretroviral drug used to treat HIV. Also the first drug to be used preventatively in people exposed to HIV (needle stick injury and mother-to-child prevention).
Emtricitabine	Also known as FTC. Frequently combined with tenofovir. The combined oral drug is known as Truvada.
Nevirapine	In addition to treating HIV, this drug is used to prevent mother-to-child transmission with a single dose to mother and infant. This regimen is now considered suboptimal.
Tenofovir	Full name tenofovir disoproxil fumarate. Also known as TDF. Used in the treatment of HIV, and in prevention in both oral form (sometimes in combination with emtricitabine) and as a microbicide gel.

Prevention trial names

ACTG-076	(AIDS Clinical Trial Group). Study that established the efficacy of a complex AZT-based regimen to prevent mother-to-child transmission of HIV. Also known as PACTG-076 ('P' for prevention').
CAPRISA 004	Trial of tenofovir gel as a vaginal microbicide in women in urban and rural South Africa. Efficacy result of 39% overall, higher in women who adhered more to the protocol (54%).
FEM-PrEP	Trial of combined oral tenofovir and emtricitabine as pre-exposure prophylaxis (PrEP) in women from Kenya, South

[1] These lists are not, and are not intended to be, comprehensive.

	Africa and Tanzania. Trial was halted due to futility; it was later found that adherence to the trial product was very low.
HPTN-052	(HIV Prevention Trial Network). This trial tested treatment-as-prevention, and reported a 96% efficacy result in 2011.
iPrEx	Trial of oral combined tenofovir/emtricitabine as pre-exposure prophylaxis (PrEP) in men who have sex with men in the Americas and South Africa. Efficacy result of 44%.
MDP-301	(Microbicide Development Program). Microbicide study that tested Pro2000 in Africa. Product found ineffective.
MIRA	Methods for Improving Reproductive Health in Africa – trial of diaphragm for HIV prevention. Product found ineffective.
Partners PrEP	Trial of oral combined tenofovir/emtricitabine and oral tenofovir as pre-exposure prophylaxis in serodiscordant heterosexual couples in Uganda and Kenya. Combined agent found 75% effective, sole agent 67% effective.
Phambili	Vaccine trial conducted in Africa that was halted when its sister study, STEP, found the product was ineffective and enhanced HIV infection in uncircumcised men.
PopART	Ongoing trial testing the implementation of the offer of male circumcision and immediate treatment for people with HIV (involves HIV testing). A cluster study, meaning that communities are randomised to receive the intervention or standard of care, rather than individuals.
TDF-2	Trial of oral combined tenofovir/emtricitabine in heterosexual people in Botswana. Found 63% effective.

RV 144	Vaccine trial that tested a combined prime and boost vaccine strategy in Thailand. Produced a marginal and contested efficacy result of 31% reduced risk of HIV acquisition.
SMART	Strategies for Management of Antiretroviral Therapy study. Tested strategic ARV treatment interruption, and found that these increased risk of disease progression/death.
START	Strategic Timing of Anti-Retroviral Treatment study.Ongoing treatment trial (in people with HIV) designed to answer the question of the optimal time top commence antiretroviral therapy.
STEP	Vaccine study conducted in the America, Europe and Australia that found the product was ineffective and enhanced HIV acquisition in uncircumcised, adenovirus 5 seropositive men.
VOICE	This study tested daily oral tenofovir, oral combined tenofovir/emtricitabine and tenofovir gel for efficacy against matched placebos. All agents found ineffective due to confounding by poor adherence through out the trial (less than a third of participants used the products). Also known as MTN 003.

Agents tested as microbicides

Buffergel	Tested for efficacy – found safe by ineffective.
Carraguard	First microbicide trial to run to full term (not halted for harm or futility). Found safe but ineffective.
Cellulose sulphate (CS)	Trial halted prematurely due to data indicating that the agent caused harm. Subsequently the difference

Nonoxynol-9	First microbicide agent tested for efficacy. Found to increase risk of HIV acquisition. Also called N-9
Pro 2000	Tested for efficacy in two trials – first trial showed marginal efficacy in an initial trial, but no efficacy in the confirmatory trial.
Savvy	Tested for efficacy, but trial halted due to futility.
Tenofovir	First antiretroviral-based microbicide. Showed 39% efficacy in initial trial, with increased efficacy in participants who adhered more closely to the protocol (54%). Had no effect in subsequent trial, which was confounded by poor adherence.

Agents/components of agents tested in vaccine trials

Adenovirus 5	A common cold virus used as a viral vector in the STEP and Phambili vaccine trials.
Rgp120	A vaccine found ineffective in 2002. Also called AIDSVAX. It was combined in a prime and boost vaccine strategy in the Thai trial RV 144 tat produced a marginally effective result.
ALVAC	Brand name of vaccine manufactured by Sanofi Pasteur.

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Preface

The idea for this thesis was born in the Hotel Ashok, New Delhi, India at the Microbicides conference in February 2008. In a cross-track session entitled, *When clinical trials end: Challenges, experiences and lessons learned,* principal investigator Lut van Damme spoke about the end of the cellulose sulphate microbicide trial. She began with an account of receiving the phone call from the chair of the Data Safety Monitoring Board and learning that – once again – the experimental product was associated with harm, and the trial would have to close prematurely. 'Once again', because Lut was also the principal investigator of an earlier microbicide efficacy trial that tested the product nonxynol-9, which had been found to enhance HIV acquisition in the trial population some seven years earlier.

Lut spoke frankly about the emotional impact of that phone call, the sense of déjà vu, her deep concern for the participants, and incredulity that such a thing could happen again despite the raft of safety studies the product had been gone through prior to large-scale efficacy testing. Then she recounted how the standard of care in this second trial – in particular the access to antiretrovirals for seroconverters – had been designed to ensure that the women had access to optimised prevention, and that anyone who acquired HIV on the trial would have access to life-saving therapy. This was delivered not in the spirit of self-justification, but as a kind of forensic examination of whether the trial had succeeded in minimising harms in the event of a worst-case scenario.

I don't recall whether Lut herself contrasted the care in the cellulose sulphate trial to the lack of access that women who acquired HIV had in the earlier nonoynol-9 study, or whether I made that connection in my head. What

impressed me was her sense of moral conviction – that research into a new HIV prevention options for women remained an imperative, and the risk this entailed for vulnerable participants had to be mitigated.

The importance of optimal standards of care was the message I took away, together with a desire to understand more about the ways that principal investigators approached standard of care issues, and how their personal experiences and convictions shaped this.

This thesis is a study of ethical issues in the standards of care in HIV biomedical prevention research, with a specific focus on the benefits for participants – the standard of prevention, ancillary care and post-trial access. The key informants are principal investigators, who are key decision makers in the research hierarchy, but who nevertheless operate within a highly controlling system of regulation, competition and funding constraints.

The community of principal investigators of HIV prevention trials is a small one, and its members evince an overwhelming commitment to the goal of developing effective, user-friendly HIV prevention modalities.

Initially I intended to triangulate the principal investigator perspectives, gleaned through interviews, surveys and personal communications, with a parallel set of data collected from members of ethics committees who reviewed HIV prevention trials. Unfortunately the response rate from ethics committee members was so low that this was unfeasible within my time constraints.

When I began this thesis in mid-2009, male circumcision was the only ‘new’ technology for prevention of sexual HIV transmission, and a series of seemingly promising interventions had produced negative results. Shortly afterwards however there were positive results from a vaccine trial, a microbicide trial, pre-

exposure prophylaxis trials and a treatment-as prevention trial. As a consequence of this dynamic environment, important normative issues about the future direction of HIV prevention research were thrown into the spotlight. Being immersed in these issues and deeply concerned about the outcomes of the ensuing debates, I responded in the series of normative papers that accompany the empirical chapters. As a result of publishing in the area that I was conducting empirical research, my relationship with some participants was altered, in that I was not viewed as a neutral interviewer but as someone associated with specific arguments about standards of care. While this affected the tenor of some interviews, I think its impact was in some ways positive. Those who disagreed with some of the arguments made had the opportunity to make their views more forcefully, and certainly one informant did so.

In terms of research contribution, I designed the surveys and the semi-structured interview format, obtained ethics approval from the University of Sydney, conducted the interviews and analysed both interview and survey data. I was the principal author of all the published papers in this thesis, and I gratefully acknowledge the intellectual input of my primary supervisor Chris Jordens, who co-authored two of the published papers and a third that is under review. My involvement with the debates around standards of prevention also facilitated productive collegiate relationships with John Kaldor, who co-authored two published articles with me, and Morenike Folayan, Catherine Hankins, Jeremy Sugarman, Sheena McCormack, Gita Ramjee and Mitchell Warren, with whom I co-authored another.

Like the principal investigators interviewed, I too share the conviction that HIV prevention research is a moral enterprise and there is an imperative to expand the range of prevention options so that people at disproportionate risk of HIV acquisition can protect themselves, and people living with HIV can protect their

sexual partners. Condoms, while necessary, are insufficient to provide protection for the myriad of ways that people connect sexually, and find themselves at risk of HIV acquisition. The field has reached a turning point – partially effective prevention interventions have been established and licensed in some places, and not in others. What happens next is that the field has to decide how these developments affect future research. This thesis, I hope, can play a part in those deliberations.

Part 1, Chapter 1

Introduction

Organisation of the Thesis

In recent years, HIV biomedical prevention has become a fast-moving field with a series of successive and at times unexpected trial results. These results have had a profound impact on thinking about the goals for future research and how that research should be conducted. In order to respond in a timely fashion to the debates engendered by new data, this is a thesis-by-publication. It comprises a series of published papers, papers accepted for publication and papers submitted for publication, which are linked into a unified whole.

These papers have been published throughout my candidature, and hence reflect the state of knowledge at the time of publication. This is noted at the beginning of chapters as appropriate.

The thesis broadly follows the traditional research reporting style, including a Background, Overview of Methods, Results and Summary and Conclusions. There is no separate Discussion section, as each of the papers has a lengthy discussion section of its own. Conclusions are drawn from these in the final section of the thesis.

In addition to material intended for publication, there are two short chapters that report findings of surveys undertaken with principal investigators who conducted HIV prevention trials and members of ethical review committees who reviewed these trials. This preliminary research provided background to focus the in-depth qualitative interviews.

Each chapter can be read as complete in its own right, and has references at the end. Published material will use the referencing style of the journal for which it was accepted. A complete alphabetical list of all references cited in the thesis is provided at the end of the thesis.

Part 1: Introduction and background

Part I has two chapters. The first introduces the issues and debates surrounding standards of prevention and care in HIV prevention research and describes the rapidly evolving evidentiary context in which this research took place. This is followed by an overview of the methods used in the thesis, which are also detailed in each of the empirical papers. It then includes the chapter *Because we can: Clashes of perspective over obligation in the failed PrEP trials*, which provides an historical account of the standard of care issue in HIV prevention research in the late1990s and how the unresolved issues re-emerged in the early to mid 2000s, when a series of HIV prevention trial sites were closed due to community concerns over the adequacy of the benefits they were providing to participants.

Part II: Empirical results

Part II is the empirical results section, which has five chapters. It begins with two short chapters that report the results of the preliminary questionnaire-based research that was undertaken with principal investigators of HIV prevention research and members of ethical review committees that reviewed it. The next three chapters are papers that draw on the empirical data from the in-depth interviews. Firstly there is *Ethics of medical care and clinical research* published online in the *Journal of Medical Ethics* Nov 22, 2012. This paper is based on informants' discussions of their perception of their role and responsibilities, and in particular discusses the issue of whether or not trial investigators have a 'doctor-like' duty of care to research participants. Secondly there is *Standard of prevention in the real world: a qualitative study of principal investigators in HIV biomedical prevention trials*, accepted for publication by *AJOB Primary Research* on February 26, 2013. This discusses how principal investigators determine appropriate standards of prevention when conducting

HIV prevention trials, and how the narrow aims and obligations of a research study sit within the broader context of disease burden and inequitable access to health care in the resource-poor world. Finally there is *Mind the gap: An empirical study of post-trial access in HIV biomedical prevention trials*, which has been submitted to *Developing World Bioethics* (under peer review). This paper provides a comprehensive empirical account of post-trial access to products shown to be successful in recent HIV prevention trials, together with provisions for antiretroviral access for trial participants who acquire HIV infection. In particular it considers the role of the researcher as an advocate for access in instances where government and regulatory authorities are slow to recognise the obligation.

Part III: Normative issues

Part III is the normative results section, and has four chapters. It begins with *Ethics of ARV-based prevention: PrEP and treatment-as-prevention*, accepted for publication in *Developing World Bioethics* on January 10, 2013. This paper explores the moral basis of two different forms of ARV-based prevention – pre-exposure prophylaxis and treatment-as-prevention – in the context of limited global resources that result in people who need ARV for their own health lacking access. This is followed by *How good is 'good enough': when should new HIV technologies should become standard of care*? published in *The American Journal of Bioethics*,2012 12(6):21-30. This chapter questions the evidentiary standards set by regulators in resource-rich countries that delay access to modestly effective products that could have major public health impact, particularly for women generalised epidemics with limited power to negotiate condom use. The third chapter is *Ethical considerations in determining standard of prevention packages for HIV prevention trials: Examining PrEP*, accepted for publication in *Developing World Bioethics* on

January 10, 2013. This chapter looks at the ethical, scientific and logistical negotiations that would be required in order to include PrEP as the new standard of prevention. The fourth and final chapter, taking into account the issues discussed in previous chapters, makes an argument that PrEp should be not the new universal standard of prevention, but the comparator against which new experimental interventions are measured. This chapter, *It's time: The case for PrEP as an active comparator in HIV biomedical prevention trials,* has been submitted to *The American Journal of Bioethics* but is still under review.

Part IV Summary and conclusions

Part IV is the summary and conclusions, which draws together the main issues in the thesis – the normative ethical conflict over ethical standards and the evidentiary debate over when and how new interventions are established as 'good enough' to constitute new standards of prevention and/or care. These are considered in the light of the different ways that informants perceive their roles with regard to different aspect of the 'standards of care' – from prevention packages for participants to post-trial access.

Introduction

Background

In 2011, an estimated 2.5 million people acquired HIV, bringing the global estimate of people living with HIV to 34 million. Eight million of these are on antiretroviral therapy, but another seven million require immediate treatment to which they do not have access. Of the 19 million remaining, they too will require treatment within the next six to ten years. While the global incidence of HIV is declining, the number of people living with HIV, and needing treatment, will continue to rise (UNAIDS 2012).

HIV prevention is a global priority, with the elimination of HIV transmission as the aspirational target – 'Getting to zero' – set by UNAIDS. Preventing new infections is critical to sustaining current treatment levels and working towards universal access.

Why prevention research is important

HIV prevention research remains imperative because, while the last five years have delivered some new, partially effective prevention interventions, there is no vaccine. Non-vaccine prevention interventions have benefits but also disadvantages, including problems with cost, acceptability, high adherence requirements (daily use or use at every coital act), levels of efficacy, and/or lack of ability to be controlled by the receptive sex partner. Until there is a highly effective, cheap and accessible intervention that does not require ongoing adherence and is suitable for both receptive and insertive sex partners, HIV prevention research will remain a high global priority.

The established ethical debates/issues concerning prevention research

There is a set of well established ethical issues in HIV prevention research. The overarching one is the 'standard of care' in clinical trials. The key point of contention is whether the standard of care for participants in a clinical trial should be the best proven prevention/treatment intervention for the illness that the trial addresses, or whether the standard may vary according to the setting in which the trial takes place. On closer examination, however, the 'standard of care' issue in HIV prevention trials actually covers a set of related issues including the following:

- Standard of prevention – the prevention package provided to all participants in an HIV prevention trial;
- Choice of comparator arm – whether an experimental intervention is measured against a placebo or an active comparator;
- Ancillary care – care that is provided to trial participants beyond that which is required for the effective conduct of the trial; and
- Access to antiretrovirals – whether or not participants who acquire HIV while on an HIV prevention trial are provided with access to ARV.

In addition to the issues that fall under 'standard of care', four other issues have become foci of ethical discourse:

- Community involvement/consultation – whether affected local communities are given the opportunity to have meaningful input into the design and implementation of research;
- Whether drug/intervention addresses a health priority in the country or countries in which the trial occurs;
- Contribution to health infrastructure – whether or how the trial contributes to local health infrastructure;

- Post-trial access – whether or not trial participants are assured access to products shown to be effective through the research.

Standard of care obligations in research are complex and multi-factorial as they straddle the health gap between the optimal access to healthcare that can be provided in a research study and real-life healthcare access and infrastructure constraints faced by the communities in which the research takes place. Accordingly standard of care is a major focus of international ethical guidance on research ethics.

Guidelines

Overview of current international guidance structures

There is no lack of authoritative normative guidance for international research ethics. The problem is that there are multiple sets of ethical guidance that propose different normative standards. The following is an overview of influential guidelines that pertain to HIV prevention research, with brief accounts of their history and key features.

Declaration of Helsinki

The initial iteration of the Declaration of Helsinki was drafted in 1964. It is a general guide to research ethics by the World Medical Association (WMA). The WMA formed after the Nuremberg Doctors' Trials specifically to articulate and protect the ethics of the medical profession. Codifying research ethics in the Declaration of Helsinki was an important aspect of that charter. The Declaration drew on the 10 points articulated in the Nuremberg Code and tied them in with physicians' obligations under the Declaration of Geneva (1948). It has since been revised six times, most recently in 2008. The 1996 revision articulated that the 'best proven' intervention should be used as a control, and that a placebo

control should not be used when a proven effective intervention existed. This clause attracted a great deal of attention in the 1997 when controversy erupted concerning research practices in HIV biomedical mother-to-child prevention research. A subsequent revision in 2000 removed the 'best proven' clause regarding placebo. The term 'best proven' was replaced with 'current', and a clause was added stipulating that trial participants should have post-trial access to the successful products of research to which they contributed. In 2002 a footnote was added specifying appropriate use of placebos that excluded HIV prevention trials ('serious or irreversible harm'), and in 2008 a new revision strengthened protections for vulnerable participants with regard to access to products proven beneficial in research and limitations on use of placebos.

The Common Rule (US Federal regulations)

The Common Rule refers to the set of federal regulations that govern federally funded clinical research in USA. Despite the Declaration of Helsinki, there were a swathe of public scandals in the 1960s over research studies that violated the principles of informed consent and minimisation of harm to research subjects. These were documented in a famous article by Henry Beecher (1966). Several years after Beecher's article, the now-notorious Tuskegee study (1937 to 1972) came to public attention. This trial withheld effective treatment from its study population of African American men in order to observe the natural history of syphilis. The Tuskegee exposé was the catalyst for sweeping reform in the United States, and it led to the National Research Act of 1974 and, subsequently, federal regulations regarding human experimentation in 1981.

CIOMS

The Council for International Organizations of Medical Sciences (CIOMS) is a non-profit non-government organisation set up in 1949 by the World Health Organization and UNESCO (the United Nations' Educational, Scientific and Cultural Organisation). CIOMS developed the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* in 1993, and revised them in 2002. These guidelines were intended to assist developing countries to define national policies on the ethics of biomedical research involving humans, to apply ethical standards in local circumstances, and to establish or improve ethical review mechanisms. The 2002 revision was catalysed by bitter disagreements within biomedicine and biomedical ethics about whether it is acceptable to use placebos in research when proven effective therapy exists.

UNAIDS/WHO

The UNAIDS/WHO guidelines specifically address the issues relating to HIV prevention trials, unlike more the general guidance offered by the Declaration of Helsinki (human subject research generally), or CIOMS (international human subject research). The UNAIDS/WHO initially published a guidance document on ethical considerations in HIV preventative vaccine research in 2000, based on consultations with a wide range of stakeholders. The document stipulates minimum ethical standards such as informed consent, use of placebos and access to ARV for seroconverters in vaccine trials. In 2007, a new guidance document, *Ethical Considerations in Biomedical HIV Prevention Trials,* was produced in concordance with a new policy that foregrounded universal access to ARV for people with HIV. The 2007 guidance document sets higher standards for research than the preceding document: it specifies that people who seroconvert during a trial must have access to ARV regimens 'from among those

internationally recognised as optimal', that the standard of prevention for all participants should be 'state of the art', and that post-trial access to effective products should be provided for trial participants and other high risk communities. In 2012, an extra guidance point was added.

HIV Prevention Trials Network (HPTN)

The HPTN guidelines are specific to HIV prevention research, like those of the UNAIDS/WHO but, unlike the latter, they are produced specifically by a US-based research network which is a subsidiary of the National Institutes of Health (NIH). Authors Stuart Rennie and Jeremy Sugarman define the HPTN guidelines as being more deliberately pragmatic that those of the UNAIDS/WHO. The guidelines divide ethical goals into 'obligatory' and 'aspirational' categories. They also define 'inequity' as differences in access to healthcare between research participants and people in the local population in which the trial is situated, rather than differences in access to healthcare between populations on a global scale (e.g. between the developing world and the wealthier nations—which is the comparison used by those who advocate a universalist, global perspective). They claim that providing an array of 'state-of-the-art' risk reduction methods that are not available outside the trial in specific contexts could constitute undue inducement to participate (Rennie and Sugarman 2010, 811).

The HPTN document also provides guidance on aspects of research not detailed in the UNAIDS/WHO document, including specifying processes of community engagement, building capacity and partnerships.

Other national/international guidelines

In addition to international guidelines produced by international non-government organisations, there are guidelines or authoritative reports on international research ethics produced by national and regional bodies. These include the US National Bioethics Advisory Commission (NBAC 2001), the UK's Nuffield Council on Bioethics (2002, 2005), the European Group on Ethics in Science and New Technologies (EGE) and the Council of Europe's Steering Committee on Bioethics (CDBI). Some institutions also have specific guidance, such as the UK's Medical Research Council's (MRC) Guidance on Provision of ART in developing countries issues, May 2003.

International Conference on Harmonisation Good Clinical Practice Guidelines (ICH-GCP)

The ICH-GCP is a set of international standards with a much broader scope than research ethics alone. The standards govern the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials, in order to ensure scientific quality and protection of the wellbeing of study participants. Adherence to GCP is mandated by many national regulatory systems (ICH-GCP 1996).

The positive trials

This study took place at a very dynamic period of HIV prevention research, 2009-2012 during which positive efficacy results were reported from six large, randomised controlled trials (RCTs) of HIV prevention interventions. One of these trials tested a candidate vaccine, RV144, while the other five tested three different, but related, preventive strategies that use antiretroviral drugs in

different ways. The CAPRISA 004 trial evaluated the topical use of tenofovir as a vaginal microbicide; the iPrEx, Partners PrEP and TDF 2 trials evaluated the efficacy of pre-exposure prophylaxis using either tenofovir alone or emtricitabine/tenofovir combined; and the HPTN 052 trial evaluated the efficacy of treatment-as-prevention (i.e. treating HIV positive people with ARV earlier than medically required in order to prevent transmission to sexual partners). These trials added to existing evidence that medical male circumcision is partially effective in reducing the rate of HIV transmission from women to men.

Of these six new results, the vaccine trial RV144 is the least significant with regard to its implications for the conduct of other studies, as its biological efficacy was both modest (below the threshold at which the country in which it was held, Thailand, would consider licensure) and contested, so it may be due to chance.

The methods and results of each of these trial is summarised below.

RV144

In October 2009, results of the RV 144 vaccine trial in Thailand were published. The investigators concluded that the vaccine lowered the rate of infection by 31.2% in the trial population of 16,402 people, based on a modified intent-to-treat analysis (an analysis that groups all participants according to the arm to which they were randomised, regardless of whether or not they remained in the trial and were vaccinated with active product or placebo according to schedule) (Rerks-Ngarm, Pitisuttithum and Nitayaphan et al. 2009). There is some controversy over the robustness of this finding, however, as the per-protocol analysis (which excludes any participant who was not fully vaccinated) returned

a lower level of efficacy and was below the level of statistical significance (Gilbert et al. 2011.)

CAPRISA 004

In July 2010 the first ever positive microbicide results was reported. The product was a vaginal gel that contained 1% tenofovir – the same antiretroviral drug used in PrEP trials. The microbicide reduced HIV acquisition by 39% overall, with higher adherers (women who used the gel 80% of the time) achieving 54% efficacy (Abdool Karim et al. 2010). CAPRISA 004 was not designed as a full scale efficacy trial, however. It included only 889 participants in the final analysis rather than several thousand, and it was not statistically powered to provide the level of evidence usually required by regulatory authorities to license a product (Abdool Karim et al 2010). Such studies are called phase IIb trials (as distinct from phase III efficacy trials), or 'proof of concept' (Bass 2004).

iPrEx

The first positive PrEP results were reported just four months after CAPRISA 004, in November 2010. The experimental intervention was TDF/FTC taken orally each day. This was found to reduce HIV acquisition by 44% (Grant et al 2010). As in the CAPRISA 004 trial, high adherers (measured by blood levels of drug) achieved greater protection: an efficacy figure of 73% to 90% is cited for those who took their pills at least 90% of the time (Grant et al 2012; Anderson et al 2012).

Treatment as prevention: HPTN 052

The strongest impact on HIV acquisition to date was seen in HPTN 052, a study in serodiscordant couples that tested the impact of earlier access to ARV for the positive partner. In couples randomised to receive immediate ARV, the negative partners were 96 % less likely to acquire HIV than in partnerships where treatment for the HIV positive member was delayed until his or her immune system showed signs of damage (CD4 counts falling below 250) (Cohen et al 2011).

Partners PrEP

The reduction in HIV acquisition seen in the Partners PrEP trial was 75%, which approximately matched the high adherers in iPrEx. Partners PrEP, reported eight months after iPrEx, was conducted in serodiscordant heterosexual couples in Kenya and Uganda (i.e. couples where one person has HIV and the other does not). It was a three arm trial, with participants randomised to TDF/FTC, TDF alone or placebo. The TDF/FTC combination showed the highest reduction in HIV acquisition, while the TDF alone arm showed 67% reduction (Baeten et al. 2012).

Botswana PrEP (TDF2)

A slightly lower level of efficacy for TDF/FTC was seen in the Botswana PrEP study – a 63% reduction in HIV acquisition. This study compared TDF/FTC to placebo in a study population of heterosexual men and women. A separate analysis aimed at differentiating between efficacy in high adherers compared with low adherers, which excluded HIV acquisitions in people on the active drug who had not taken their pills for 30 days or more when seroconversion

occurred, showed a 78% reduction (Thigpen et al. 2012). The Botswana PrEP results were reported at the same time as the Partners PrEP trial.

Other relevant research with positive findings

PACTG 076

The first evidence that ARV could be used to prevent HIV transmission was published in 1994 (Connor, Sperling and Gelber et al. 1994). The study, known as PACTG076, reduced transmission from HIV infected mothers to their infants by two thirds, using the single antiretroviral drug AZT during pregnancy and delivery, administering the drug to infants after delivery for six weeks, and replacing breast milk with formula. This study, which was conducted in the US and France, transformed the care of HIV positive pregnant women in high income countries. The regimen was criticised as being unachievably costly and complex for use in low income countries, however. The ethical furore that ensued as a result of mother-to-child transmission studies in low income countries proceeding as if there was no proven effective intervention will be discussed in detail in Part 1 Chapter 2.

Male circumcision

After the mother-to-child trials, and before any ARV-based prevention strategy was proven effective, male circumcision was shown to reduce the rate of HIV transmission from women to men. Three separate randomised controlled trials showed that the ancient practice of surgical removal of the foreskin of the penis[1] had a protective effect of around 55% in heterosexual men living in countries

[1] Circumcision to prevent HIV transmission is medical procedure, as distinct from traditional practices, as serious safety problems related to the ritual form of circumcision.

with generalised epidemics (Auvert et al. 2005; Bailey et al. 2007; Gray et al. 2007).

Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis (PEP) was instituted in medical settings (needle stick injuries and the like), following a case-control study published in 1997 that showed an 81% reduction in HIV acquisition associated with PEP (Cardo et al. 1997). Randomised controlled trials were never conducted for either medical or sexual exposure, as to randomise a person to placebo given the evidence that could be extrapolated from peri-natal trials (in particular Wade, Birkhead, Warren et al. 1998) was deemed neither feasible nor ethical (van den Berg, Lindenburg and Coutinho 2010, 324; Poynten et al. 2012).

Other relevant trials with negative findings

FEM-PrEP

Amidst the positive trial results of biomedical HIV prevention in 2010-11, one trial bucked the trend. Fem-PrEP, a trial of combination TDF/FTC in women at high risk of HIV from the African countries, was prematurely halted by its Data Safety Monitoring Board (DSMB) due to futility in April 2011 (CDC April 11 2011). DSMBs are independent, expert groups who are charged with reviewing data at pre-ordained intervals (or in response to unexpected adverse events) to ensure participant safety and adherence to the trial protocol.

The DSMB determined after an interim analysis that the trial would not be able to demonstrate efficacy if it continued for the pre-ordained time. Why this PrEP result differs from the two other PrEP studies that involved heterosexual women

(Partners PrEP and Botswana PrEP) is considered to be at least in part due to very low adherence on the study (Van Damme et al. 2012).

VOICE

Final results of the VOICE trial (also known as MTN 003) were presented on March 4, 2013. The findings were all negative – that is, none of the three interventions tested were found to be effective in the trial population: combination oral PrEP (TDF/FTC), TDF-only oral PrEP, and tenofovir gel (vaginally delivered, using a different dosing strategy to CAPRISA 004). The failure was attributed to low adherence to all interventions on the trial: on average, less than 30% of women randomised to each of the intervention arms had detectable blood levels of the respective drugs (29% for tenofovir/emtricitabine, 28% for oral tenofovir, and 22% for tenofovir gel).

VOICE tested the three different prevention strategies against matched placebo (both an oral and a vaginal placebo were used). It was a phase IIb study rather than a full scale phase IIIb efficacy trial, powered to show efficacy of more than 25% of the study products, with efficacy of less than 25% the null hypothesis (Protocol v 2 December 31 2010, 10.3, p. 9).

In 2011, two of the three active arms of the VOICE trial were stopped due to futility[2]. This judgement was made by the DSMB on the basis that these particular active arms could not show efficacy even if they proceeded.

[2] 'Futility' in this context meaning that the control arm and the intervention arm have nearly identical results, and even if the trial continued a statistically significant difference between the two would likely not occur.

The VOICE trial is endpoint-driven, with its final endpoint being 217 HIV infections in the study population. Under the protocol, the DSMB was to review data when 25%, 50% and 75% of these 217 seroconversions occurred.

Earlier negative trials: microbicides and diaphragm

Before 2007 there was a raft of failures of new technologies designed to prevent sexual transmission of HIV, and some interventions were found to enhance HIV acquisition.

The first failed trial in the microbicides field was a trial of nonoxynol-9, a spermicide that had showed promising anti-HIV activity. The product was evaluated in a population of sex workers, but it was halted prematurely by its DSMB in 2000 when more HIV infections were observed in the active (experimental) arm of the trial than the placebo arm. It was found that frequent use of the product increased the risk of HIV infection by disrupting the vaginal epithelium (van Damme et al. 2002).

Following the nonoxynol-9 results, several other microbicide candidates were tested for efficacy, including Savvy, Carraguard, cellulose sulphate (CS), Buffergel and Pro 2000. The Savvy trial was halted in 2006 when the HIV incidence in the trial population was significantly lower than expected. The DSMB determined that the trial could not reach a result (i.e. it was deemed ‘futile’).

Two parallel trials of the microbicide cellulose sulphate were halted in 2007, when an interim analysis showed that results in one of the trials were trending towards the nonoxynol-9 pattern – that is, increased seroconversions in the

active product arm suggested that the product was increasing than decreasing the risk of infection. While in the final analysis this trend was not statistically significant, the researchers concluded that the product may have caused harm, and research on the product ceased (van Damme et al. 2008).

Following the premature closure of the four preceding microbicide trials, the fact that the Carraguard study was completed in full was considered a victory in itself, despite the fact that the product, while safe, did not show any efficacy (Skoler-Karpoff et al. 2008).

The run of negative results was continued by the MIRA (Methods for Improving Reproductive Health in Africa) trial, which tested whether the diaphragm provided protection from HIV acquisition for women living in South Africa and Zimbabwe. The trial showed no additional protective effect from the diaphragm, though the authors suggest that some effect may have been seen with a different trial design or higher levels of adherence to the study product (Padian et al. 2007).

A small proof-of-concept study, HPTN 035, tested two candidate microbicides Buffergel and PRO2000, with results released in February 2009. Buffergel was ineffective, but PRO 2000 appeared to be about 30% effective (MTN 2009). In December 2009, however, results of a much more robust trial MDP 301 also testing PRO 2000 showed no impact on HIV acquisition (AVAC 2009).

Previous vaccine trials

Prior to RV144, two candidate vaccines failed to show efficacy in large-scale trials. The first was rgp120, a vaccine based on the envelope protein of HIV. Two variants of rgp120 were trialled in different populations in the early 2000s – gay men, men who have sex with men and so-called 'high risk' women in Europe and North America tested the variant designed for subtype B (Flynn et al. 2005), while a Thai trial tested a variant based on prevalent Thai subtype B/E in injecting drug users (Vanichseni et al. 2004).

Despite neither of these trials testing rgp120 showing efficacy, the rgp120 vaccine formed part of the subsequent 'prime/boost' vaccine strategy, RV 144, that produced the borderline result described on page 17. The RV 144 trial essentially used two different vaccines in sequence – rgp 120 and an ALVAC vaccine based on a canary pox vector – each of which aimed to stimulate different aspects of the immune system.

A different vaccine strategy, aimed at producing cell-mediated immunity was tested by the pharmaceutical company Merck. This trial, known as the STEP study, used a human adenovirus as a vector and had sites in the Americas, Europe and Australia. It not only failed to show efficacy, but uncircumcised men and those with pre-existing immunity to the vector (adenovirus 5) were more likely to become infected than those on placebo, suggesting the vaccine enhanced infection in these populations (Buchbinder, Mehrotra & Duerr 2008).

A second efficacy trial of this vaccine (Phambili) ceased recruitment following on the STEP results. It was conducted in South Africa, and only 801 of the projected 3000 people were enrolled at the time recruitment closed.

PrEP trials prior to 2010

In the early 2000s, four trials of tenofovir-only pre-exposure prophylaxis (PrEP) were commenced in Africa and Asia. One trial had sites in Ghana, Cameroon and Nigeria, while the other three were limited to sites in a single country: Thailand, Cambodia and Malawi. By 2006, the two trials in Cambodia and Malawi had closed, as had two of the sites (Cameroon and Nigeria) in the international African study (Page-Shafer et al. 2005; Haire 2011). The international study produced a statistically non-significant result in 2007 (Peterson et al 2007), while the Thai study went ahead despite serious ethical objections, and is still ongoing at the time of writing (March 2013) (Chua et al. 2005).

The controversy over the early PrEP trials centred on two key issues in the conduct of HIV prevention research: whether or not host communities are meaningfully engaged in research so that they can have input into research design and implementation, and the putative obligation of researchers and sponsors to ensure access to ARV for seroconverters.

These issues are discussed in full in Part 1 Chapter 2, *Because we can: Clashes of perspective over research obligation in the failed PrEP trials*. This situates the PrEP trials in the historical context of the vertical transmission debates of the 1990s, where there was protracted disagreement over the use of placebos despite the existence of a proven intervention. It then discusses how research practice has been influenced by the dramatic improvement in the clinical management of HIV from 1996 onwards, and the treatment access movement.

Context - vulnerability to HIV infection

HIV prevention trials are conducted in HIV negative individuals from high incidence populations, the majority of which are in low to middle-income countries in Africa (and to a lesser degree, Asia) that have generalised HIV epidemics. A smaller proportion of high incidence populations are drawn from countries with epidemics that are concentrated with populations that face a disproportionately high risk of HIV acquisition, such as in gay men and other men who have sex with men, and injecting drug users.

The HIV prevention trial context is one in which participants are vulnerable to risks of a structural, social and medical nature (Abdool Karim and Abdool Karim 2012). Structural risks include the disproportionate risk of HIV which renders them eligible for trial participation. Social risks include being identified with a stigmatised infection that is associated with other stigmatised identities such as homosexuality or sex work. Medical risks include harm caused by the product under investigation. Benefits for participants can include better general medical care (either directly or through referrals), improved access to HIV prevention interventions, improved access to antiretroviral therapy (ARV) if HIV is acquired, strengthened medical and research infrastructure at community level, and post-trial access to proven products.

The level at which benefits are provided to participants, who is responsible for providing which benefits, and whether benefits should be provided to participants alone, the trial community more broadly, or somewhere in between, are issues contested at the theoretical level. They are also vexed at implementation level, because regulatory constraints, funding limitations and

feasibility confounders all affect both what is possible and what is deemed desirable within a trial.

Aims/Research questions

This study aims

- To gather evidence about how benefits to participants are negotiated in efficacy trials of biomedical HIV prevention technologies.
- To re-consider the debates about obligations to trial participants in the light of the positive trial results (what are the ethical issues in HIV prevention research in the age of partially effective HIV prevention modalities?)
- To understand how principal investigators and ethics committees navigate this territory, and how experience in conducting HIV prevention trials shapes views on how they should be conducted in the future
- To explore the factors that affect how and when positive research findings are implemented; and
- To account for any ethical issues that emerge in the empirical investigations that are not present in the current normative literature.

Methods

This study addressed HIV prevention efficacy trials (phase IIb or III) that took place between 2000 and 2011. It has both empirical and normative components.

Empirical components of the study

In all, 28 efficacy trials of biomedical HIV prevention (either phase III or IIb) were identified between 2000 and 2011through the Current Controlled Trials

and clinical trials.gov databases. Principal investigators and first authors of key publications were contacted by email and invited to participate in the study by completing the questionnaire, and/or participating in a semi-structured interview.

Surveys

Principal investigators and first authors of key publications were contacted by email and invited to participate in a survey. The survey was a preliminary form of data collection that aimed to make initial contact with principal investigators and gather general information about standards of care.

Members of ethical review committees that had reviewed phase IIb or phase III HIV prevention trial were also contacted by email and invited to participate in a survey. Originally this survey too was intended as a preliminary form of data collection that would provide guidance for in-depth qualitative interviews. Accessing and recruiting REC personnel proved slow and unproductive. Many REC chairs did not respond at all, and those that did respond indicated that they were either ineligible or unwilling to participate. No single individual agreed to be interviewed, so this aspect of the study was abandoned in order to meet timelines.

In addition, the response to the REC survey was extremely poor – out of 69 eligible RECs, responses were received by only 15 eligible respondents and only 11 completed the survey. Due to this low response, survey results will not be published, however the survey instrument and responses are available in Appendix D.

Interviews

I interviewed 14 principal investigators from the 28 trials identified. Between them they had worked on more than 20 HIV prevention trials. Both men and women were included in the sample. Of the principal investigators interviewed, two were 'in-country' investigators, which means that they headed the study at a particular trial site, but did not have oversight of the trial as a whole. The remaining 12 informants oversaw whole trials and in some cases networks of HIV prevention trials. Most of these informants had been a principal investigator or a senior member of the research team on more than one study.

All of the interviews were conducted by the author. Nine interviews were conducted by telephone and five were conducted face-to-face. The study was reviewed and approved by the ethics committee of the University of Sydney. Data were coded using N-Vivo 9 software and analysed thematically.

Data were analysed from a symbolic interactionist perspective, in which interviews are understood not as mirror images of an objective reality (the positivist view), but as accounts of experience through which participants in the interview purvey their understandings of the social world under investigation (the 'world' of the HIV prevention trial).

Additional data collection

Ongoing email contact was established with principal investigators of HIV prevention trials (including some who did not consent to be interviewed), and information was exchanged about specific aspects of their respective studies, with particular regard to post-trial access issues. Trial protocols were obtained where possible, research network websites were checked regularly and

correspondence established with trial-related public relations personnel. Advocacy networks including AVAC (AIDS Vaccine Advocacy Coalition), the International Rectal Microbicides Advocates (IRMA) and the former Global Campaign for Microbicides (GCM, now defunct), were also sources.

Normative component

The normative component of the study focuses on four "big-picture" issues.

The first normative issue is whether there is ethical justification for antiretroviral (ARV)-based prevention in HIV endemic areas. The answer to this cannot be assumed, given limited health budgets, difficulties with targeting ARV-based prevention, adherence issues and the interconnectedness of ARV-based prevention and treatment. Seven million people who require ARVs cannot access them, so there is an argument that ARV should not be used as prevention until all who require treatment have assured access.

If ARV-based prevention is not ethically justifiable, or if only some forms of it are justifiable and others are not, this raises a serious issue for HIV prevention research. If ARV-based prevention *is* justifiable, then there is an argument that it should be provided, particularly in jurisdictions where the right to health is explicitly stated. This issue is explored in Part 3 Chapter 1, *Ethics of ARV-based HIV prevention: treatment-as-prevention and PrEP*. This paper investigates the rights claims of uninfected people for access to ARVs for prevention, and whether moral claims justify the provision of ARV therapy to those who do not yet clinically require treatment as a way of reducing HIV transmission risk. It compares the application of PrEP and treatment-as-prevention strategies using a

public health stewardship model developed by the Nuffield Bioethics Council and the Beauchamp and Childress principles approach (1994).

The second normative issue is how the positive HIV prevention trial results – which demonstrate *partial* efficacy – affect (or should affect) future HIV prevention research. The key issue is what level of evidence is required to disturb equipoise, and whether or not the urgency with which interventions are required has an impact. This is discussed in Part 3 Chapter 2, *How good is "good enough"? The case for varying standards of evidence according to need for new interventions in HIV prevention*.

The third normative issue is whether the newly-validated modality of pre-exposure prophylaxis (PrEP) should be now become standard of prevention. The implications are discussed with respect to normative guidance, scientific rationale, policy and considerations regarding affected communities. These questions are considered in Part 3 Chapter 3, *Ethical considerations in determining standard of prevention packages for HIV prevention trials: Examining PrEP***.**

The fourth normative issue is whether PrEP should become the comparator arm in HIV prevention trials from now on. This is discussed in Part 3 Chapter 4, which considers different sets of normative research ethics guidelines and the moral imperative to ensure that there are not double standards between low-to-middle and high income countries, with regard to where PrEP should sit in the current standard of care.

Results

Empirical

Three key publications, together with chapters outlining the survey results, form the basis of the empirical results.

Standard of prevention in the real world: A qualitative study of principal investigators in HIV biomedical prevention trials

This chapter looks at how principal investigators on HIV prevention studies determine appropriate standards of prevention. It builds on previous work mapping standards of care in HIV prevention trials by investigating how decisions were arrived at, in addition to reporting what was decided. The analysis shows that there is no ethical consensus about the standard of prevention among principal investigators, and that rational arguments are used to support disparate positions.

Ethics of medical care and clinical research: A qualitative study of principal investigators in biomedical HIV prevention research: This chapter is a response to Miller and Brody's (2003, 2007) critique of the 'therapeutic obligation' in research. It considers whether the views of the principal investigators are compatible with the proposition that there is a "doctor-like" duty of care to research participant. It finds that these particular researchers do admit this obligation, though it is limited by the nature of the research, the depth of the relationship between research and participant, and the capacity of the research site. The paper concludes that the therapeutic orientation in HIV prevention trials appears to be indivisible from competent research practise by making concrete and appropriate benefits available to trial participants and their communities, which support rather than compete with local infrastructure.

Mind the gap: An empirical study of post-trial access in HIV biomedical prevention trials: This chapter provides an empirical, descriptive account of post-trial access to successful biomedical HIV prevention interventions and ARV for seroconverters**.** It elucidates the constraints that trial investigators face in when securing 'post-trial' access and analyses the procedural problems that beset the implementation of normative frameworks on post-trial obligations outlined in guidance documents. Finally recommendations are made as to how the other critical actors – sponsors and governments/regulators – should contribute to securing this benefit.

Normative

Ethics of ARV-based HIV prevention: Treatment-as-prevention and PrEP

This chapter argues that the use of ARV for prevention is ethically justified, despite imperfect global access to drugs for those in clinical need, and that there are sound moral reasons for implementing both PrEP and treatment-as-prevention. The determination of which ARV-based HIV prevention strategy is ethically preferable in particular settings maybe complex and must take into account both public health and interpersonal considerations.

How good is "good enough"? The case for varying standards of evidence according to need for newiInterventions in HIV prevention

This chapter argues that the judgments of evidentiary standards are not value-neutral. It discusses two of the recent positive trials (CAPRISA 004 and iPrEx) as case studies. It first considers the question of whether equipoise still exists regarding the respective interventions (tenofovir gel and emtricitabine/tenofovir PrEP). It then addresses the question of whether the regulatory decision to

require further confirmatory trials, which will potentially delay access to scientific innovation to the people who are most urgently in need of it.

Ethical considerations in determining standard of prevention packages for HIV prevention trials: Examining PrEP

This chapter outlines arguments concerning the inclusion of newly established ARV-based HIV prevention interventions as standard of prevention in HIV prevention trials from multiple perspectives. It argues that there is a clear need to incorporate stakeholders in a robust discussion to determine the appropriate trial design for each study population.

It's time: The case for PrEP as an active comparator in HIV biomedical prevention trials

This chapter argues that in light of evidence that treatment-as-prevention, PrEP and circumcision are effective in preventing HIV acquisition, it is no longer ethically appropriate to design HIV prevention without securing access to these interventions, particularly as each of these strategies has been approved by a regulatory authority or in a normative guideline. Given that many important scientific questions about the optimal use of existing prevention technologies that remain to be answered, however, this chapter also argues that PrEP should form the comparator against which new experimental HIV prevention technologies should be tested.

Conclusions

This thesis addresses critical issues in the ethics of HIV prevention trials. The experience of the failed PrEP trials in the early 2000s demonstrates the need for meaningful community collaboration with researchers in order build trust and

produce better outcomes for the communities who participate in research. I argue in favour of ARV-based prevention using a range of modalities, not restricted to either treatment-as-prevention or PrEP alone, on the grounds that different individuals and populations have different prevention needs. The high bar set for product licensure is questioned in the context of generalised epidemics, based on the modelled impact of less effective strategies in high incidence areas and the moral right of people to make use of technology to protect their health.

This thesis catalogues differences in scope, duration and timeliness of post-trial access to effective products of research, so that lessons can be learned about the effective mechanisms for distribution of newly validated products, and the role of principal investigators in advocating for justice in this respect is acknowledged.

Despite the current consensus on the basic prevention package (condoms, counselling and STI treatment)[3] there remains serious disagreement as to whether packages should be optimised or basic, linked to national guidelines or universal standards. This has potential to result in ethical stalemate or double standards in an age where new partially effective HIV prevention technologies are licensed for use in some countries only, as we now see in the case of PrEP. The argument that PrEP should now be added to the prevention package for all experimental interventions, while attractive in terms of distributive justice, is defeated by the spectre of drug-drug interactions while antiretroviral-based

[3] Voluntary medical male circumcision, as will be shown, has not been universally offered to date in trials with eligible participants (HIV negative, heterosexually active, uncircumcised men from countries with generalised epidemics).

interventions remain the most promising, and by the issues of scale it would necessarily involve. Accordingly, I propose that PrEP should be used as a universal comparator until there is a more effective and user-friendly biomedical intervention for HIV negative people.

Overview of empirical methods

There were four components to the empirical data collection:

1. Surveys of principal investigators (PIs) who had conducted phase IIb or III HIV biomedical prevention research between 2000 and 2011;
2. A survey of members of ethics committees who had reviewed phase IIb or III trials of HIV biomedical prevention research between 2000 and 2011;
3. In depth semi-structured interviews with PIs who had conducted phase IIb or III HIV biomedical prevention research between 2000 and 2011;
4. Additional data collection through email communications.

Principal investigator survey

The survey was a preliminary form of data collection intended to make initial contact with principal investigators, to gather general information about standards of care, and to identify ethical review committees eligible to participate in the survey of ethics committee members.

Principal investigator eligibility

PIs were considered eligible for the study if, between 2000 and 2011, they had conducted a phase IIb or III trial of a biomedical intervention that was designed to prevent sexual transmission of HIV.

To identify the study population, I searched the Current Controlled Trials and clinical trials.gov databases for trials that were conducted between 2000 and 2011 using the term ‘HIV prevention’. I then sorted through the search results to identify phase III or IIb trials that evaluated the efficacy of biomedical interventions designed prevent sexual transmission of HIV. Twenty-eight trials met these

criteria. Principal investigators (PIs) and first authors of key publications from these trials were contacted by email and invited to participate in the study by responding to an online survey and/or participating in an in-depth interview.

Principal investigator recruitment

Eligible PIs were contacted by email and sent information forms and a link to the online survey. Potential participants were also followed up in person at international conferences (Microbicides 2010 in Pittsburgh, International AIDS Society in Rome and Microbicides 2012 in Sydney) and through mediated email introductions and recommendations provided by colleagues. Each eligible PI was sent at least one reminder email.

Principal investigator questionnaire design

The questionnaire was designed using SurveyMonkey Select software. The conceptual framework was based on categories established in a seminal 'standards of care' mapping study (Heise, Shapiro and West Slevin 2008). The questionnaire was piloted online with two staff members and three students at the Centre for Values Ethics and the Law in Medicine (VELiM) and went live in May 2010. Initial responses from eligible PIs highlighted some further difficulties with the questionnaire design, particularly the requirement that people repeat the questionnaire several times depending on the number of trials they had conducted. Accordingly, the study was re-designed and piloted again with two members of the ethics committee of ACON (formerly known as the AIDS Council of NSW) and two staff members from the Kirby Institute. Following feedback, further alterations were made to the format, the wording, and the sequence of questions, and provision was made within the questionnaire to report on more than one study.

Because it was difficult to recruit PIs to the study, those who responded to the initial questionnaire were not asked to complete the revised one, and results of both the initial survey and the revised survey are reported. The survey used a multiple choice format, with some questions allowing a single response and others allowing more than one, depending on the nature of the question. In many cases, a free text field was also provided for further comment. Descriptive statistics in the form of simple frequencies were calculated for responses to closed-ended questions, and summaries were compiled for free-text responses where they were provided.

Data collected from both the initial survey and the revised, final survey are reported alongside each other. I have noted when the survey questions differed. Where difference makes the two sets of results incommensurable, they are reported separately.

Ethics committee member surveys

The survey of ethics committee members was also intended as a preliminary step for in-depth qualitative interviews. Accessing and recruiting ethics committee personnel proved slow and unproductive, however. The interviews were therefore abandoned. Fifteen eligible participants began the online survey, and eleven completed it, from a potential 69 eligible RECs. This response is too low to merit publishing the results.

Principal investigator interviews

Forty-two principal investigators and first authors of key publications from these trials were identified, contacted by email, and invited to participate in a semi-structured interview. Two were uncontactable. Repeated invitations were sent in

order to recruit investigators who had worked on multiple studies. Potential participants were also followed up in person at international conferences (Microbicides 2010 in Pittsburgh, International AIDS Society in Rome and Microbicides 2012 in Sydney) and through mediated email introductions and recommendations provided by colleagues. Each eligible PI was sent at least one reminder email. Some eligible individuals did not respond, some declined, and one agreed to an interview but was subsequently uncontactable.

Fourteen principal investigators from the 28 trials identified were interviewed, who between them had worked on more than 20 HIV prevention trials. Both men and women were included in the sample. Of the principal investigators interviewed, two were 'in-country' investigators, meaning that they headed the study at a particular trial site, but did not have oversight of the trial as a whole. The remaining 12 informants oversaw whole trials and in some cases networks of HIV prevention trials. Most of these informants had been a principal investigator or a senior member of the research team on more than one study.

I personally conducted and coded all of the interviews. Nine interviews were conducted by telephone and five were conducted face-to-face. The study was reviewed and approved by the ethics committee of the University of Sydney. Data were coded using N-Vivo 9 software and analysed thematically.

Data were analysed from a symbolic interactionist perspective, in which interviews are understood not as mirror images of an objective reality (the positivist view), but as accounts of experience through which participants in the interview purvey their understandings of the social world under scrutiny - the 'world' of the HIV prevention trial (Miller and Glasner 2004).

The interviews were conducted from May 2010 to March 2012, a period during which five of the nine successful HIV biomedical prevention trials had positive findings (CAPRISA 004, iPrEx, HPTN 052, Partners PrEP and TDF-2). In several cases, the positive trial results were known by the informant but not by the interviewer.

Where interview data were factual (as distinct an expression of an opinion), facts were verified against other sources, such as protocols if available and trial websites.

Additional data collection

Ongoing email contact was established with principal investigators of HIV prevention trials (including some who did not consent to be interviewed), and information exchanged regarding specific aspects of their respective studies, with particular regard to post-trial access issues.

Principal investigators (PI) of the nine HIV prevention trials that reported positive efficacy findings were contacted by emails for fact-checking and to supply additional information. This group included PIs who had been interviewed and those who had not. In one instance the PI referred me to another senior member of the research team for further details.

PIs who had not been interviewed were engaged in email exchanges on post-trial access issues. Of the nine positive trials, two PIs did not respond either to requests for an interview or to provide email comments. In these cases (the RV144 vaccine trial and the Orange Farm circumcision trial), information about post-trial access

plans was sourced from pre-trial documents and post-trial access meeting minutes provided by AVAC (AIDS Vaccine Advocacy Coalition) and by a trial-related public relations officer.

Trial protocols were obtained where possible; research network websites were checked regularly, and correspondence established with trial-related public relations personnel. Information was also gleaned from advocacy networks including AVAC (AIDS Vaccine Advocacy Coalition), the International Rectal Microbicides Advocates (IRMA) and the former Global Campaign for Microbicides (GCM, now defunct.

References

Abdool Karim, Q., S. S. Abdool Karim, J. A. Frohlich, et al. 2010. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 329 (5996):1168-1174.

Anderson, P.L., D. V. Glidden, A. Liu, et al. 2012. Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men. *Science Translational Medicine* 4 (151):151ra125

Auvert, B., D. Taljaard, E. Lagarde, Joëlle Sobngwi-Tambekou, Rémi Sitta, and Adrian Puren. 2005. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLoS Med* 2 (11):e298

Baeten, J. M., D. Donnell, P. Ndase, et al. 2012. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine* 367 (5):399-410.

Bailey, R.C, S Moses, C.B Parker, et al. 2007. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 369:643 - 656.

Beauchamp, T., and J. Childress. 1994. *Principles of biomedical ethics*. 4th ed. New York, Oxford: Oxford University Press. Original edition, 1979.

Beecher, H. K. 1966. Ethics and Clinical Research. *New England Journal of Medicine* 274 (24):1354-1360.

Buchbinder, S.P., D. V. Mehrotra, A. Duerr, et al. 2008. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *The Lancet* 372 (9653):1881-1893.

Cardo, D. M., D. H. Culver, C. A. Ciesielski, et al. 1997. A Case–Control Study of HIV Seroconversion in Health Care Workers after Percutaneous Exposure. *New England Journal of Medicine* 337 (21):1485-1490.

Council for International Organizations of Medical Sciences (CIOMS). 2002. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available at: http://www.cioms.ch/publications/layout_guide2002.pdf Accessed 23 March 2013.

Cohen, M. S., Y. Q. Chen, M. McCauley, et al. 2011. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine* 365 (6):493-505.

Connor, E. M., R. S. Sperling, R. Gelber, et al. 1994. Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. *New England Journal of Medicine* 331 (18):1173-1180.

Council of Europe's Steering Committee on Bioethics (CDBI). Available at: http://www.coe.int/t/dg3/healthbioethic/cdbi/default_en.asp Accessed 23 March 2013.

European Group on Ethics in Science and New Technologies (EGE). Available at: European Group on Ethics in Science and New Technologies Accessed 23 March 2013.

Flynn, N. M., D. N. Forthal, C. D. Harro, et al. 2005. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *The Journal of infectious diseases* 191 (5):654-65

Gilbert, P.B. J.O. Berger, D. Stablein, et al. 2011. Statistical Interpretation of the RV144 HIV Vaccine Efficacy Trial in Thailand: A Case Study for Statistical Issues in Efficacy Trials. *Journal of Infectious Diseases* 203: 969-975.

Gray, R.H., G. Kigozi, D. Serwadda, et al. 2007. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *The Lancet* 369:657 - 666.

Heise, L., K. Shapiro, and K. West Slevin. 2008. Mapping the Standards of Care at Microbicide Clinical Trial Sites. Washington DC: Global Campaign for Microbicides.

International Conference on Harmonization Good Clinical practice (ICH-GCP). 1996. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf Accessed 23 March 2013.

Medical Research Council (MRC). 2003. Policy on antiretroviral therapy (ART). Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002455

Accessed 23 March 2013.

Medical Research Council (MRC). 2004. Research Involving Human Participants in Developing Societies. Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002461

Miller, J. and B. Glasner. 2004. The "Inside" and the "Outside": Finding realities in interviews in D. Silverman (ed) *Qualitative Research: Theory, Method and Practice*. London: Sage, 2004: 125-129

National Bioethics Advisory Commission (NBAC). 2001. Ethical and policy issues in international research: Clinical trials in developing countries. Bethesda, Maryland. Available at: http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf Accessed 23 March 2012.

Nuffield Council on Bioethics. 2007. *Public health: ethical issues*. Chapter 2 (An Ethical Framework) Available at: http://www.nuffieldbioethics.org/sites/default/files/files/Public%20health%20Chapter%202%20-%20An%20ethical%20framework.pdf Accessed 23 March 2013.

Nuffield Council on Bioethics. 2005. The ethics of research related to healthcare in developing countries: a follow-up discussion paper. Out of print.

Poynten, I.M., Jin, F., Mao, L.,et al. 2009. Non-occupational postexposure prophylaxis, subsequent risk behaviour and HIV incidence in a cohort of Australian homosexual men *AIDS* 23 (9):1119-26.

Rennie S, J. Sugarman and the HPTN Ethics Working Group. 2009. HIV Prevention Trials Network Ethics Guidance for Research, HIV Prevention Trials Network.

Rennie, Stuart, and Jeremy Sugarman. 2010. Developing ethics guidance for HIV prevention research: the HIV Prevention Trials Network approach. *Journal of Medical Ethics* 36 (12):810-815.

Rerks-Ngarm, S., P. Pitisuttithum, S.Nitayaphan, et al. 2009. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *New England Journal of Medicine* 361(23):2209-2220.

Skoler-Karpoff, S., G. Ramjee, K. Ahmed, et al. 2008. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. *The Lancet* 372:1977 - 1987.

Thigpen, M. C., P. M. Kebaabetswe, L.A. Paxton, et al. 2012. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *New England Journal of Medicine* 367 (5):423-434.

UNAIDS. 2012a. Global report: UNAIDS report on the global AIDS epidemic 2012. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf Accessed 30 January 2013.

UNAIDS/ World Health Organization (WHO). 2012 b (English original 2007, additional guidance point added 2012).UNAIDS／07.28E／JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS／WHO Guidance Document. Geneva: UNAIDS and World Health Organization. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf [Accessed 18 Feb 2013].

van den Berg,C., K. Lindenburg, R. Coutinho. 2010. In *Modern infectious diseases epidemiology: concepts, methods, mathematical models and public health*,

edited by M. K. Alexander Krämer, Klaus Krickeberg. New York, Dordrecht, Heidelberg, London: Springer.

Vanichseni, S., J.W. Tappero, P. Pitisuttithum, et al. 2004. Recruitment, screening and characteristics of injection drug users participating in the AIDSVAX(R)B/E HIV vaccine trial, Bangkok, Thailand. *AIDS* 18 (2):311-316.

Wade NA, Birkhead GS, Warren BL, et al. 1998. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *New England Journal of Medicine* 339:1409--14. .

World Medical Association (WMA). 1948. *Declaration of Geneva*. Available at: http://en.wikipedia.org/wiki/Declaration_of_Geneva Accessed February 6, 2013.

World Medical Association (WMA). Declaration of Helsinki. 1964; as amended in 2008. Available at: http://www.wma.net/en/30publications/10policies/10about/index.html Accessed 30 January 2013.

Part 1, Chapter 2

Because we can: Clashes of perspective over researcher obligation in the failed PrEP trials

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Keywords: HIV prevention research, standard of care, researcher obligation, pre-exposure prophylaxis, bioethics, developing world.

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Abstract

This article examines the relationship between bioethics and the therapeutic standards in HIV prevention research in the developing world, focusing on the closure of the pre-exposure prophylaxis (PrEP) trials in the early 2000s. I situate the PrEP trials in the historical context of the vertical transmission debates of the 1990s, where there was protracted debate over the use of placebos despite the existence of a proven intervention. I then discuss the dramatic improvement in the clinical management of HIV and the treatment access movement, and consider how these contexts have influenced research practice. I argue that as HIV prevention trials oblige researchers to observe the rate at which vulnerable people under their care acquire HIV, there is an obligation to provide antiretroviral treatment to seroconverters and other health care benefits that fall within the scope of researchers' entrustment, both to avoid exploitation and to enact reciprocal justice. I argue against propositions that the obligations to provide specific benefits are vague, fall only upon researchers and sponsors, and create injustices by privileging the few over the many. Finally, I contend that the realisation of a broader standard of care in HIV prevention research broadens the role of research from being a simple tool to produce knowledge to a complex intervention that can play a part in the reduction of health disparities.

Introduction

This article focuses on the closure of the pre-exposure prophylaxis (PrEP) trials in the early 2000s and reflects on how the issues of justice and exploitation in clinical research played out in a context where HIV treatment activism had affected the landscape of possibility.

It is my contention that unresolved issues concerning the obligations of HIV prevention researchers to research participants resurfaced in the context of the PrEP trials. The issue debated in the late 1990s was the use of placebo controls in vertical transmission research, which left the research community divided as to the nature and scope of researcher obligation. The issues that arose in the PrEP trials are closely related: concerning ancillary care, compensation for harm and access to antiretroviral therapy for seroconverters. Rather than being another academic debate, however, communities became actively engaged in the question of what clinical research could, or should, offer to participants.

The PrEP controversy erupted seven years after the exposé in the *New England Journal of Medicine* about mother-to-child (vertical) HIV transmission trials which were placebo-based despite the existence of a proven intervention.[1]

[1] P. Lurie & S.M. Wolfe. Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries. *N Engl J Med* 1997; 337: 853-856; M. Angell. The Ethics of Clinical Research in the Third World. *N Engl J Med* 1997; 337: 847-849.

PrEP – pre-exposure prophylaxis – is an HIV prevention strategy, as yet unproven, that involves the use of antiretroviral medication prior to exposure to prevent HIV infection.[2] This article looks at three PrEP trials that came to international attention: one that was to be conducted in Cambodia in a population of female sex workers; a second at three sites in Africa: Ghana, Nigeria and Cameroon, in a population of women at high risk of HIV infection; and a third in Thailand in injecting drug users. By 2005, the Cambodian trial and two of the three African trial sites had closed due to community objections to the conduct of the research, and activists were raising serious concerns about the Thai study. While there were differences in the specific issues at the respective sites the overwhelming concerns were access to treatment and/or prevention interventions, and medical care as part of the research package.[3]

Both the failed PrEP trials and the earlier placebo-controlled vertical transmission trials raise important ethical questions for researchers. What obligations do researchers have to participants? What role does context and circumstance play in determining obligation? How do ideas of fairness and reciprocity play out in the context of limited research funding and inadequate national health systems? I will argue that the researcher is obliged to protect the best interests of the research participants, insofar as these interests fall within the scope of the

[2] E. Mills et al. Designing Research in Vulnerable Populations: Lessons from the HIV Prevention Trials that Stopped Early. *Br Med J* 2005; 331: 1403-1406.

[3] E. Mills et al. Media Reporting of Tenofovir Trials in Cambodia and Cameroon. *BMC International Health and Human Rights* 2005; 5 no. 6.

Available at: http://www.biomedcentral.com/1472-698X/5/6 [Accessed 13 Jan 2010].

research study and to the extent that logistics allow. This obligation, arising from the imperative to avoid exploitation and grounded in reciprocal justice, should take precedence over the production of knowledge and potential benefits that may flow from this knowledge. In the case of HIV prevention studies, this may necessarily involve investment in infrastructure to facilitate treatment access post-trial. While this arguably increases the burdens placed upon researchers, it situates the production of knowledge appropriately within a relationship of care for the subject, rather than divorcing the research context from the clinical context.

The debate over placebo controlled vertical transmission trials

The issue of therapeutic standards in HIV prevention research came into sharp focus in 1997, when the *New England Journal of Medicine* published an article by Lurie and Wolfe,[4] which condemned a series of clinical trials in the developing world as unethical. The basis of their criticism was that interventions to prevent vertical (mother-to-child) transmission of HIV were being tested against placebo controls, despite the existence of a proven regimen established in 1994, known as the '076 regimen', named after the landmark trial ACTG076.[5] Their critique was supported by an editorial by Marcia Angell,[6] which compared the vertical

[4] Lurie & Wolfe, *op. cit*. note 1.

[5] E.M. Connor et al. Reduction Of Maternal-Infant Transmission Of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994; 331: 1173-1180.

[6] Angell, *op. cit.* note 1.

transmission trial to the infamous Tuskegee experiment, which denied African American men access to proven syphilis treatment in order to study the natural history of the disease.

The practice of testing a new therapy against placebo when a proven therapy exists was explicitly proscribed by the *Declaration of Helsinki* (the 'Declaration'),[7] an international document providing guidance on research ethics. The *Declaration of Helsinki* was adopted in 1964 by the World Medical Association and periodically updated. It is a descendent of the *Nuremberg Code* of 1949, which defined guidelines for the ethical conduct of human research in the aftermath of the trials of the Nazi doctors, but is somewhat more liberal than that code in its definitions of permissible research.[8]

Because the 1996 Declaration explicitly stated that placebo-controlled trials where proven interventions exist were unethical, it came under intense scrutiny and was subject to a number of revisions, which have been dealt with elsewhere.[9] In the wake of this scrutiny, there ensued an international debate about research standards and the role of guidelines. The debate

[7] World Medical Association (WMA). 1996. *Declaration of Helsinki 1996*. Ferney-Voltaire, France: WMA. Available at: http://www.jcto.co.uk/Documents/Training/Declaration_of_Helsinki_1996_version.pdf [Accessed 22 Sept 2010]

[8] B. Loff & J. Black. The Declaration of Helsinki and Research in Vulnerable Populations. *Med J Aust* 2000; 172: 292-295; H. Wolinsky. The Battle of Helsinki. *EMBO Rep* 2006; 7: 670-672.

[9] See for example, R. Macklin. After Helsinki: Unresolved Issues in International Research. *Kennedy Inst Ethics J* 2001; 11: 17-36.

centred upon the themes of exploitation, the obligations of researchers to trial participants, the need for research to be responsive to the needs of the developing world and the requirement for scientific rigour.[10] These issues were not resolved,[11] and they resurfaced in a different guise with regard to the ethical design of the PrEP trials.

The HIV treatment revolution and its impact

While the ethical debate over placebo-controlled trials in the developing world was raging in the journals, the landscape of HIV treatment (for those who could afford it) was being transformed in the clinics of the developed world. Research first presented in 1996, and consolidated in the years immediately following, radically changed the perception of HIV/AIDS as a terminal illness in wealthy countries. It was shown that HIV replication could be effectively suppressed using combination antiretroviral therapy (ART), and that this appeared to halt and even reverse immune damage in people with HIV. Although initial optimism about the possibility of a cure turned out to be misplaced, the prediction that HIV

[10] Angell, *op. cit.* note 1; Lurie & Wolfe, *op. cit*. note 1; R. Levine. The Need to Revise the Declaration of Helsinki. *N Engl J Med*, 1999; 341: 531-534; H.E. Varmus & D. Satcher. Ethical Complexities of Conducting Research in Developing Countries. *N Engl J Med* 1997, vol. 337:1003-1005.

[11] Macklin, *op. cit*. note 9.

infection could become another chronic manageable condition has arguably come to pass – for some people and to some extent.[12]

By July 2000, at the International AIDS Conference in Durban, South Africa, the stark injustice of people dying of AIDS in the developing world while people lived indefinitely with HIV in the resource rich world was palpable. Treatment access had become the most significant political issue.[13] The drug pricing policies and intellectual property regimes that made treatment inaccessible for the majority of people living with HIV became the news story from this conference, rather than some biomedical breakthrough.[14]

Only two antiretroviral drugs were listed on the World Health Organization's (WHO) essential drug list in 2000 and these were both listed for prevention rather than treatment (AZT and nevirapine - both to prevent vertical transmission). Even Bactrim, the basic

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[12] K. Bhaskaran. Changes In The Risk Of Death After HIV Seroconversion Compared with Mortality in the General Population. *JAMA* 2008; 300: 51-59; The Antiretroviral Therapy Cohort Collaboration. Life Expectancy of Individuals on Combination Antiretroviral Therapy in High-Income Countries: A Collaborative Analysis of 14 Cohort Studies. *Lancet* 2008; 372: 93-299.

[13] See for example, B. Whyte. Nelson Mandela Calls for Unity at the XIIIth International AIDS Conference in Durban, South Africa. *B World Health Organ* 2000; 78 (9): 1169. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2560854/pdf/0042-9686_78_9_1169a.pdf [Accessed 21 Feb 2010].

[14] N. Geffen.2000. What Happened in Durban? A South African Perspective. *The Body* September/October. Available at: http://www.thebody.com/content/art13213.html [Accessed 21 Feb 2010].

antibiotic used to prevent two common opportunistic infections in people with AIDS, was grossly underutilised in Africa.[15]

Five major pharmaceutical companies announced a partnership with UNAIDS to reduce drugs costs for Africa at the Durban conference,[16] but this news was greeted by activists with 'caution and scepticism', due to concerns that such programs would come with complicating conditions that could prevent access to generic antiretrovirals.[17]

By 2003, the treatment access movement that had begun at the grass roots and non-governmental organization (NGO) levels went mainstream. The WHO announced its '3 by 5'

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[15] South African Department of Health. 2000. *Report on the 13th International AIDS Conference, Durban, 9 – 14 July 2000: Summary Report of Major Issues, Conclusions and Recommendations*. Pretoria, South Africa: South African Department of Health: section 7.3. Available at: http://www.doh.gov.za/aids/docs/13conf00.html [Accessed 21 Feb 2010].

AIDS Coalition to Unleash Power (ACT-UP) New York. 2000. *WHO Sold Out to Big Pharma*. New York, NY: ACT-UP New York. Available at: http://www.actupny.org/reports/durban-who.html [Accessed 3 Mar 2010]; D.G. McNeill. 2000. Agencies Urge Use of Affordable Drug for H.I.V. in Africa. *New York Times* (online) 6 April. Available at: http://www.nytimes.com/2000/04/06/world/agencies-urge-use-of-affordable-drug-for-hiv-in-africa.html?pagewanted=1 [Accessed 13 Jan 2010].

[16] A. Diarra. Making a Public-Private Partnership Work - An Insider's View. *B World Health Organ* 2001;79: 795-796.

[17] ACT-UP, *op. cit.* note 15; J.S. James. Access to Treatment Worldwide: From Talk to Action at Durban. *Aids Treatment News* 2000; #347. Available at: http://www.aegis.org/pubs/atn/2000/ATN34703.html [Accessed 21 Feb 2010].

program, which framed universal access to HIV treatment (and prevention), for those who needed it, as a human right. Its specific target was to gain ART for three million people by the year 2005. While this target was not reached, the program developed policy and infrastructure that greatly facilitated later scale-up. In addition to addressing barriers like distribution and pricing, this program devised simplified systems of ART prescription that required minimal health service support. This assisted in removing structural barriers to access.[18]

Two other international events had major impacts on access to ART. The first was the United Nations General Assembly Special Session on AIDS (UNGASS 2001), which spawned the Global Fund for AIDS, Tuberculosis and Malaria. The second was the President's Emergency Fund for AIDS Relief (PEPFAR), first announced in the United States President's State of the Union address in 2003.

From being considered untenable in resource-poor settings, ART was now hailed as 'an appropriate, rational and cost-effective investment choice for developing countries'.[19]

[18] WHO-UNAIDS. 2005. *The 3 by 5 Initiative: Treat three million people with HIV/AIDS by 2005*. Geneva, Switzerland: WHO. Available at: http://www.who.int/3by5/en/ [Accessed 21 Feb 2010].

[19] J.P. Moatti et al. Antiretroviral Treatment for HIV Infection in Developing Countries: An Attainable New Paradigm. *Nat Med* 2003; 9: 1449-1452.

The role of community protest in the PrEP trial closures

Having foreshadowed the failure of the PrEP trials due to community protest, I will now discuss in more detail the circumstances under which the trials were closed, the issues raised by protesters and how these concerns relate both to the bioethical discourse about standard of care and the political movement for universal treatment access.

Four different clinical trials of the experimental HIV prevention strategy known as 'PrEP' had begun by 2005, with sites in Africa and Asia, and with planning underway for further trials in the Americas. All of the trials investigated the safety and/or efficacy of the antiretroviral drug tenofovir,[20] in preventing HIV infection.[21] The rationale for the number of trials was the need to explore the intervention in a variety of high risk contexts (i.e. in sexual activity, both gay and straight, and injecting drug use) and in different genders and body types.[22]

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[20] Later trials added the drug emtricitabine (FTC) combined with tenofovir in a single tablet, under the brand name Truvada. See for example listings on trial registries, available at: http://www.controlled-trials.com/mrct/trial/438173/%27HIV+infection%27+AND+prevention [Accessed 3 Mar 2010].

[21] AIDS Vaccine Advocacy Coalition (AVAC). 2005. Will a Pill a Day Prevent HIV? New York, NY: AVAC. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/3116 [Accessed 13 Jan 2010]; A. Forbes. Moving Towards Assured Access to Treatment in Microbicide Trials. *PLoS Med* 2006. 3 (7): e153: 980-983.

[22]K. Page-Shafer et al. HIV Prevention Research in a Resource-Limited Setting: The Experience of Planning a Trial in Cambodia. *Lancet* 2005; 366:1499-1503.

Three of these trials became the focus of adverse attention: the Cambodian trial in female sex workers, the African trial in high-risk women with sites in Cameroon, Nigeria and Ghana, and the Thai trial in injecting drug users. The fourth trial, studying tenofovir in high risk 'men who have sex with men' (MSM) in Malawi, was terminated without fanfare for reasons that remain unpublished. Allegations were made that the trials were unethical on the basis of not collaborating sufficiently with communities, providing selective and biased information about potential adverse effects, and being unwilling to provide comprehensive health insurance for participants.[23] Each trial had a US sponsor: the Cambodian trial was sponsored by the United States'(US) National Institute of Allergy and Infectious Diseases (NIAID) and Family Health International (FHI); the African trial again by FHI and the Thai trial by the US Centers for Disease Control and Prevention (CDC).[24]

US sponsorship was the root cause of unrest in the Thai trial, as it targeted injecting drug users. According to the *Declaration of Helsinki* 2000, participants in a drug trial should be assured of the best current prophylactic method – meaning in this instance, clean injecting equipment. The US, however, neither acknowledged the 2000 version of the Declaration nor would its government allow the provision of injecting equipment. Bleach was provided to

[23] Mills et al. *op. cit.* note 2; Mills et al. *op. cit.* note 3.

[24] While the Cambodian study was sponsored by FHI, its funding was provided by a direct grant from the Bill and Melinda Gates Foundation. See Page-Shaffer et al. *op. cit.* note 22.

clean equipment, but this is sub-optimal; the US claims that its actions are in line with Thai policy, were disputed.[25]

The Cambodian trial

In Cambodia the contentious issues were: concerns about the long-term safety of tenofovir in HIV negative people; access to care, especially ART, post-trial; the level of HV prevention counselling to be provided to participants; pre- and post-test HIV counselling; and the limited involvement of the community in the study design.[26] In particular, the issue of compensation was extremely problematic. Under US law research sponsors are not required to provide free medical care or compensation for participants injured in clinical research.[27] Although medical care would be available for participants from the research facility for the duration of the trial, it was unclear whether prospective participants understood this, and at any rate there was no provision for medical care after the trial, apart from access to ART for seroconverters through the then-fledgling national program. It is not clear that the preferential access to ART

[25] A. Chua et al. The Tenofovir Pre-Exposure Prophylaxis Trial in Thailand: Researchers Should Show More Openness in Their Engagement with the Community. *PLoS Med* 2005; 2: 1044-1045.

[26] Page-Shafer et al. *op. cit.* note 22, p. 1499; A. Forbes & S. Mudaliar. 2009. *Preventing Prevention Trial Failures: A Case Study and Lessons for Future Trials from the 2004 Tenofovir Trial in Cambodia.* Washington, DC: Global Campaign for Microbicides; 12. Available at: http://www.global-campaign.org/clientfiles/Cambodia.pdf [Accessed 28 Apr 2010].

[27] R. Steinbrook. Compensation for Injured Research Subjects. *N Engl J Med* 2006; 354: 1871-1873.

for trial participants was well understood, as access to ART was cited as a key issue by protesters.

Adverse effects of the study drug, especially potentially serious long-term ones, became a very significant focus of attention for the prospective study participants, who were often the sole breadwinner for families, the survival of whom depended on the commercial sex worker being fit for work.[28]

The problem of compensation was apparent to the study investigators early on, as Page-Shafer et al. note in their *Lancet* article:

> During 2003, we consulted with [other] investigators who had faced similar issues in other developing countries, and considered various options for the assistance of people with long-term health problems that could be attributed to their participation in trials, including insurance schemes, lump-sum payments, and the establishment of long-term contracts for the provision of clinical services. None of these options fits with the policies of our funding agencies.[29]

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[28] Tenofovir Trial in Cambodia, film, directed by Women's Network for Unity. Cambodia: Women's Network for Unity, 2008. Available at: http://www.drpetra.co.uk/blog/womens-network-for-unitys-account-of-the-tenofovir-trial then go to: http://blip.tv.file/1418090 [Accessed 3 Mar 2010]; J. Fawkes. The Cambodian PrEP Trial: The Sex Workers' Perspective. Powerpoint presentation to *The 2nd Symposium on Microbicides and HIV Biomedical Prevention*, Sydney, 14 July 2008.

[29] Page-Shafer et al. *op. cit.* note 22.

Tensions between the researchers and the sponsors are evident in the above quotation, and also in a later comment that in response to rising evidence of misinformation about the trial in the community, the two universities collaborating in the study – the University New South Wales and the University of California – sought to place the trial protocol on their respective websites, but were denied permission to do so by the sponsors.[30]

Of note, it was not merely access to ART for seroconverters that the Cambodian sex workers sought,[31] – as mentioned above, arrangements for access had been made by the investigators, with ART supplied in line with the WHO guidelines for treatment in resource-limited settings.[32] The workers also sought ways to manage the risk of long term illness or injury caused by the experimental drug.[33]

In a short documentary film, *Tenofovir Trial in Cambodia*,[34] made from the perspective of the sex worker group Women's Network for Unity, it is clear that the prospective participants

[30] Page-Shafer et al. o*p. cit.* note 22.

[31] Weijer and Le Blanc (2006) discuss the Cambodia trial as if this were the sole reason for the protest. Other sources quoted in note 25 attest that a major concern was long-term health issues resulting from a trial related injury – in particular, from kidney damage. See C. Weijer & G.J. LeBlanc. The Balm of Gilead: Is the Provision of Treatment to those Who Seroconvert in HIV Prevention Trials a matter of Moral Obligation or Moral Negotiation? *J Law Med Ethics* 2006; 34.4: 793ff.

[32] Forbes, *op. cit*. note 26.

[33] Ibid.

[34] Tenofovir Trial in Cambodia, o*p. cit.* note. 28.

believed that the trial would expose them to significant harms, such as the possibility of requiring new kidneys due to drug toxicity. While in some respects such a fear is disproportionate (tenofovir has an excellent safety profile compared with other antiretrovirals), it underscores the difficulties of communicating clearly and honestly about issues like risk across the vast epistemic divide between researchers and very poor women with minimal access to education, whose very daily survival appears to depend upon being sceptical.

The specific demand made by the Women's Network for Unity was for health insurance to cover any potential long-term adverse events from the trial drug (referred to in the film as 'life' insurance),[35] for a period of 30 to 40 years post-trial. What they were offered instead was US$3 per month for participation.

Tenofovir Trial in Cambodia does not distinguish between misinformation, conspiracy theories[36] and the substantive issue of fair compensation for trial harms. Where it succeeds, is in foregrounding the profound depths of exploitation, trickery and violence to which these women have been subjected, which makes their level of suspicion of authority all too understandable. Extreme poverty, gang rape, systemic discrimination and abandonment by NGOs - that obediently dropped work with sex worker groups so as to meet the requirement

[35] Forbes & Mudaliar, *op. cit.* note 26, p. 13.

[36] Conspiracy theories presented included a belief that sex workers were deemed expendable people upon whom dangerous drugs could be tested with impunity.

for getting US funding during the George W. Bush Administration – form the background for negotiations.[37]

In a memorable riposte, one Cambodian sex worker in the film dismisses the charge that the action of the Women's Network for Unity has denied her a chance to contribute to humanity. 'What has humanity ever done for me?' she asks.[38]

Trust – identified by the investigators as a key component in working with communities – would be an elusive commodity, and deservedly so.[39] Indeed, the record of drug companies in providing reasonable access to drugs to the populations in which they (the drugs) were tested is not good: in Brazil, where the human papilloma virus (HPV) vaccine was tested, it is now sold at higher price than in the US.[40]

On August 13, 2004 the Cambodian Prime Minister, Hun Sen, put an end to the trial (which had ethics approval in Cambodia, Australia and the US), stating that: 'Cambodian people are not waste, and Cambodia is not a waste bin', and researchers should take their trials

[37] Forbes & Mudaliar, *op. cit*. note 26, pp. 9-10

[38] Tenofovir Trial in Cambodia, o*p. cit.* note. 28.

[39] B. Loff et al. Unethical Clinical Trials in Thailand: A Community Response (letter). *Lancet* 2005; 365: 1618-1619.

[40] J. Beloqui. 2008. *International Rectal Microbicides Advocates* (listserv communication). Philadelphia, PA: Critical Path Project. Available at: http://critpath.org/pipermail/rectalmicro_critpath.org/2008-November/000564.html [Accessed 13 Jan 2010]

elsewhere.[41] Of note however, the sex workers had indicated a willingness to continue negotiations, so long as they were party to the decision-making processes from the earliest stages and their lives and wellbeing were considered appropriately in the development of the research design.[42]

The African trial sites

Six months after the termination of the Cambodian trial, the Cameroon site of the African PrEP trial was halted by the Minister of Public Health. Activist concerns were related to: the level of HIV prevention counselling provided – there were only eight counsellors for 400 women, the lack of female condom provision (only male condoms were provided) and alleged inadequate preparation for ART provision. Indeed, the informed consent document explicitly stated that the trial would not provide ART to seroconverters, a stance that was informed by the notion that supplying ART in a context where it was not generally available would constitute undue inducement.[43] Trial seroconverters would be referred to existing NGO sources, which the activist group ACT-UP Paris described as overburdened, with treatment provision for 10,000 individuals, while 40,000 people were already in need.[44]

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[41] Loff et al. *op. cit.* note 40.

[42] Ibid.

[43] E. McGrory, A. Irvin & L. Heise. 2009. *Research Rashomon: Lessons from the Cameroon Pre-exposure Prophylaxis Trial Site*. Washington, DC: Global Campaign for Microbicides - PATH: 27. Available at: http://www.global-campaign.org/clientfiles/Cameroon.pdf [Accessed 5 May 2010].

[44] ACT-UP Paris. 2008. *ACT-UP-Paris and Treatment Activism*. Paris, France: ACT-UP Paris. Available at: http://www.actupparis.org/article3482.html [Accessed 12 May 2009].

In addition to these substantive concerns, Mills et al.[45] cite widespread, inaccurate rumours that the investigators would deliberately inject participants with HIV, or that the tablets themselves contained HIV. These rumours appear to have their provenance in an argument advanced by the activist group ACT-UP Paris, who were involved in the protests, that the provision of inadequate HIV prevention counselling to participants was a backdoor method of increasing HIV infection in the cohort.

Following an inquiry, the Ministry of Public Health issued a number of administrative requirements, including formal site accreditation and more regular reporting. The trial, however did not resume. A month later, the Nigerian trial site closed after it was determined that the site did not comply with operational and laboratory procedures.

In 2006, data from the Ghanaian site alone from the African trial was reported at the International AIDS Conference in Toronto, Canada. Tenofovir appeared to be safe in HIV negative people, results showed, but the sample size was too small to show statistically significant efficacy.[46]

[45] Mills et al. o*p. cit.* note 2.

[46] L. Peterson et al. Tenofovir Disoproxil Fumerate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. *PLoS Med* 2007; 2: e27.

The Thai trial

Despite significant disquiet about ethical issues, the Thai PrEP trial targeting injecting drug users, which opened in 2005, has not stopped. The Thai Drug Users' Network and the Thai AIDS Treatment Action group cite as ethical violations, the failure to provide participants with sterile injecting equipment, lack of meaningful community consultation, lack of commitment from the sponsors to promoting the safety of participants enrolled in the trial, assured access to tenofovir for participants for one year only post-trial and no agreement to work with the Thai Ministry of Public Health towards securing price reductions of tenofovir after the trial.

The lack of consultation with communities and the failure to negotiate access to the experimental product, if effective, flouts both the letter and the spirit of key guidance documents.[47] The failure to provide sterile injecting equipment, however, is most problematic

[47] Such as Guidelines 11,12 and 13 of the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* 2002, available at: http://cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm [Accessed 3 Mar 2010]; Articles 6,17, 32 and 33 of the Declaration of Helsinki 2008, available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf [Accessed 3 Mar 2010] and Guidance points 4, 5 13 and, depending upon the contested legality, 14 of the UNAIDS Ethical Considerations in HIV Preventive Vaccine Research 2000, available at: http://data.unaids.org/publications/IRC-pub01/JC072-EthicalCons_en.pdf [Accessed 3 Mar 2010]. It should be noted that the 2002 UNAIDS guidelines do not discuss provision of established HIV behavioural prevention such as condoms and clean injecting equipment under standard of care requirements, rather they position it as 'risk reduction measures' under 'informed consent' and only require provision of clean injecting equipment where it is legal to do so. The later UNAIDS guidelines, Ethical

because it is an established, effective intervention,[48] which reliably reduces HIV acquisition in this population. Non-provision exponentially increases the likelihood of seroconversions during the trial and thus exploits participants' vulnerability to HIV acquisition by denying them a proven intervention.

The reason for the lack of sterile injecting equipment is contested: the CDC website claims it is the result of Thai government policy, but this is vigorously denied in correspondence appearing in *The Lancet* that claims there is no such Thai policy; instead it is suggested that it was the US government policy which precluded provision (this was changed in 2009 with the sweeping changes brought in by the Obama administration).[49]

Regarding ART provision, there is a national treatment program in Thailand, but the Thai Drug Users' Network claims systemic discrimination toward drug users by that service, and that very few of the 50,000 Thais on ART are injecting drug users.[50]

Considerations in Biomedical HIV Preventions Trials (2007) adopts a new category 'standard of prevention' (Guidance point 13) to define the control arm in HIV prevention trials. Available at: http://data.unaids.org/pub/Report/2007/jc1399_ethical_considerations_en.pdf [Accessed 24 Sept 2010]

[48] This is the language used in the CIOMS guidelines regarding placebo use. Guideline 11, CIOMS, *op.cit.* note 44.

[49] S. Jintarkanon et al. Unethical Clinical Trials in Thailand: A Community Response (letter). *Lancet,* 2005; 365: 1617-1618.

[50] K. Alcorn. 2005. Thai Tenofovir Trial Runs into Trouble after Ethics Protests from Drug Users. *NAM Aidsmap* 10 March.Available at: http://www.aidsmap.com/en/news/AF0B8B91-A54B-4632-9736-03F66FE37CF5.asp

Given the strength of the ethical objections to the Thai trial, it seems remarkable that it has remained open, and continues recruiting, while the other trials closed. As to the reason why, I can only guess that this is concerned with the illegality of drug use in Thailand: Chua et al.[51] mention that long prison terms and even the death sentence are norms for drug-related offenses. Police have wide discretionary powers, and there have been an alleged 3,000 extra-judicial executions[52]. These factors arguably add up to a population who will not want to make too much fuss or attract too much attention for fear of reprisal.

The impact of the activism

The activism surrounding the PrEP trials has generally been met with disapproval from the wider community of people involved in HIV research. Joep Lange, who co-chaired the fifteenth International AIDS Conference in Thailand, which was disrupted by PrEP trial protesters, claimed that the activist group ACT-UP Paris, in particular, used methods of 'uninformed demagogy [and] intimidation'.[53] Lange's anger at the failure of the PrEP trials is based on three key issues: the demonstrated need for new biomedical HIV prevention

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[Accessed 14 Jan 2010].

[51] Chua et al. *op. cit*. note 25.

[52] ibid

[53] J.M. Lange. We Must Not Let Protestors Derail Trials of Pre-Exposure Prophylaxis for HIV. *PLoS Med* 2005; 2 (9): 833-834. Available at:

http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.0020248

[Accessed 13 Jan 2010]

strategies, which he deems to be foiled by the trial closures; the fact that it is demonstrable that the researchers in the Cambodia trial did, in fact, consult with community groups (but arguably not the right groups, and not well enough); and thirdly, that the protests were led from outside, motivated by the 'misguided ethical imperialism' of ACT-UP Paris.[54] While it is undeniable that there were elements of sensationalism and misinformation in the protests, this does not mean that there were no substantive issues involved. As the measured analysis written by the investigators from the Cambodia trial makes clear, the issue of compensation for harms was pertinent, but the trial sponsors would not negotiate.[55]

During the controversy over the design and implementation of PrEP trials, provision of ART for seroconverters was treated as one of several requirements to ensure that participants got fair recompense for their participation. The sex workers involved in the protests were more interested in health care generally, particularly in the event of a catastrophic side effect like kidney failure, than ART alone. This demand for fair access to ongoing healthcare made by the PrEP protesters demonstrates a concept of equity at work, one where people – including trial participants – are assumed to have the same basic rights to life saving treatment regardless of where they live. This, of course, is a tenet of the treatment access movement: that universal access is a human right.

[54] Ibid.

[55] Page-Shafer *op. cit*. note 22

The experience of the PrEP trials shows that even very vulnerable populations have an expectation that if they undertake risks, they earn an entitlement to benefits that comprehensively offset those risks. Further, that they should be consulted in the determination of the nature of those benefits.

The bioethics response to the universal access movement

Although access to ART in the developing world remains inadequate, the universal access movement has created political impetus to redress this and programmatic interventions to facilitate it. These changes create the context where it can be argued that obligations to research participants have changed due to external circumstances. This fits with the tenet that 'we can only morally require of people to do what they are capable of doing, or what it is reasonable to ask',[56] commonly expressed as 'ought implies can'. The argument that treatment provision in prevention trials is too burdensome, while always contestable, is now clearly untenable.

Ruth Macklin (2006) contends that arguments against obligatory provision of ART in prevention trials were based on the assumption that either the researcher or the sponsor would have to bear the cost. Now that treatment access programs are in place and partnerships between treatment and research programs are being forged, that assumption has been

[56] R. van der Graaf & J.J.M. van Delden. What is the Best Standard for the Standard of Care in Clinical Research? *Am J Bioethics* 2009; 9(3): 35-43.

overturned. Within the new context of treatment access programs, she suggests an obligation to provide ART has arisen.[57]

The problem for bioethics becomes how to theorise the source of the obligation. The obligation is not grounded in compensatory justice, argue both Slack et al.[58] (2004) and Weijer and Le Blanc,[59] as HIV acquisition is not caused by trial participation but by risk behaviour, against which participants are explicitly counselled. Causation is a necessary condition of compensatory claims. If the prevention technology itself does not cause the HIV infection (so the argument goes), then the infection arises from the participant's own behaviour.

The individualism that underpins this argument and the avoidance of addressing the structural determinants of HIV risk is problematic.[60] An eighteen year old sex worker who has unprotected sex in Durban, South Africa has a much greater risk of being infected with HIV than her sister in Sydney Australia would have. Women and men who exchange sex for money, goods or favours may also have less control over the sex they have, including

[57]R. Macklin. Changing the Presumption: Providing ART to Vaccine Research Participants. *Am J Bioethics* 2006; 6:W1–W5.

[58] C. Slack et al. Provision of HIV Treatment in HIV Preventive Vaccine Trials: A Developing Country Perspective. *Soc Sci Med* 2005; 60(6): 1197-1208.

[59] C. Weijer & G.J. LeBlanc. *op. cit.* note 31.

[60] D. Zion. HIV/AIDS Clinical Research, and the Claims of Beneficence, Justice and Integrity. *Camb Q Healthc Ethics* 2004;13: 404-413.

whether or not condoms are used. A trade-off between accepting more money for an unprotected sex act may appear a good deal to someone who is struggling to survive from day-to-day. The riposte to this point is that the researchers are not responsible for this inequity. This is true, but it is also true that they gain by it, because HIV prevention trials must instrumentalise the vulnerability of people who are at high risk of HIV to run successful trials. Weijer and Le Blanc argue that HIV prevention researchers are people 'already contributing importantly to redressing injustice'.[61] This contains an implicit claim that research is in itself a moral enterprise. Even if you take this claim to be uncontested (which it is not), it overlooks the fact the research is an industry – one that uses people as a raw material. This arguably creates an obligation on the part of researcher to provide a benefit that is commensurate with the risk, inconvenience and level of gratitude owed to those who participate in such significant research.

The assertion that HIV acquisition is not causally connected to experimental biomedical agents is problematised by the examples of two recent – and possibly three - prevention trials in which the experimental technologies specifically increased, rather than diminished, biological susceptibility to HIV infection. Three trials in the last decade have been stopped by their Data Safety and Monitoring Boards due to increased susceptibility to infection in the active treatment group, and in two of these cases it was found that the experimental agent increased the likelihood of seroconversion.[62] These trials are an important reminder of the

[61] C. Weijer & G.J. LeBlanc. *op. cit.* note 31.

[62] Briefly, two experimental microbicides (topical agents designed to be used in the vagina to prevent infection) have caused an increased rate of HIV infection in women using the product in clinical trials testing their efficacy

risk of participating in clinical research and the possibility of unintended and unexpected effects when experimental products are used in the broader populations in efficacy trials.

However, to argue that the basis of an obligation is risk alone, underestimates the responsibilities of the physician/researcher and the inescapable obscenity that the success of HIV prevention trials depends upon recruiting people sufficiently vulnerable to HIV acquisition (due largely to structural factors beyond their control), and observing the rate at which they acquire this life-threatening infection.

Belsky and Richardson provide a moral framework for determining the care that should be provided to trial participants beyond that which is required for the successful conduct of a study.[63] They argue that participants in clinical research entrust their health to researchers in a 'partial and limited' manner which creates a corresponding duty of care. Analysis of this, together with analysis of the strength of the claim, allows distinctions to be drawn.

(see below); L. Van Damme et al. (on behalf of the COL-1492 study group). Effectiveness of COL-1492, a nonoxnol-9 Vaginal Gel, on HIV-1 Transmission in Female Sex Workers: A Randomized Controlled Trial. *Lancet* 2002; 360 (9338): 971-977; L. Van Damme et al. Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission. *N Engl J Med* 2008; 359 (5): 463-472; One vaccine trial has shown increased susceptibility to HIV associated with the product in certain populations; S.P. Buchbinder et al. Efficacy Assessment of a Cell-mediated Immunity HIV-1 Vaccine (the Step Study): A Double-blind, Randomised, Placebo-controlled, test-of-concept Trial. *Lancet* 2008; 372: 1881-1893.

[63] L. Belsky & H. Richardson. Medical Researchers' Ancillary Clinical Care Responsibilities. *BMJ* 2004; 328: 1494–1496.

Although the scope of this partial entrustment will vary, it is possible to generalise. As a participant typically gives permission for a disease under study to be monitored, the scope of the entrustment typically includes caring, as needed, for that disease. Since participants' permission is needed for doing tests or collecting confidential medical information, the scope of entrustment typically includes following up on any clinically relevant information or diagnoses generated.[64]

The determination of obligation, they claim, depends upon a condition being within the scope of entrustment and the obligation being sufficiently strong. There are four tests of the strength of the claim. These are questions of the degree of the participant's vulnerability, the depth of the relationship between the participant and the researcher (meaning intensity and duration - is the study a one-off test or of an ongoing nature), the degree of gratitude the researcher owes the participant and consideration of whether there are important reasons against providing the care. They illustrate this with the example of a woman in a trial of a vaginal microbicide, who is found to have vaginal thrush, and who appears to have dental problems. The researcher is obliged to treat the first condition, as its diagnosis is made through an assay used in the research, and vaginal health is a significant factor in a trial that alters the vaginal environment. Her dental condition, however, falls outside the scope of entrustment because its diagnosis does not arise from 'exercising the permission participants grant on entering the study'.[65]

[64] Ibid: 1495.

[65] Ibid.

Applying this framework to HIV prevention trials, randomised controlled trials (RCTs) require seroconversions in order to get results, and HIV testing occurs as part of the trial. As Richardson points out in his later article, this places treatment for HIV centrally within the scope of entrustment, and establishes a presumptive duty of care.[66] HIV prevention trials in developing countries involve people who are highly vulnerable, and they necessarily instrumentalise the socio-economic vulnerability of research subjects to HIV to produce a result. Trial participation requires long-term commitment with relatively frequent clinical contact. Participation involves risk due to the exposure to an agent that has been used in relatively few people and the seroconversion of a percentage of trial participants are foreseeable harms, necessary to the research and over-determined by circumstance. The participants' agreement to volunteer for the trial provides researchers with a significant opportunity. The researchers, science and society all benefit from successful HIV prevention trials, but unless ART is provided for seroconverters and appropriate general health care to all participants, no commensurate benefit is provided to the participant. The degree of dependence upon the researcher is likely to be high given poor health infrastructure. Hence, all the conditions for determining that there exists a strong claim are present.

[66] H. Richardson. Gradations of Researchers' Obligation to provide Ancillary Care for HIV/AIDS in Developing Countries. *Am J Public Health* 2007: 97(11): 1958

Finally it needs to be considered whether there is an important reason not to provide ART. Prolonging the lives of otherwise healthy people who are in their most productive years provides a strong moral imperative for ART. The point that providing therapy for some members of a community but not others introduces a new level of advantage and disadvantage in an important one, because justice and equity are central aims of the enterprise.[67] It is not sufficient, however, to deny research participants a justifiable claim to life saving treatment. Some degree of priority-setting and rationing is unavoidable in ratcheting up universal ART programs in resource-poor areas. Prioritising research participants in government or donor-funded facilities is appropriate, as research participants remain citizens and human beings to whom both governments and aid organizations have responsibilities. However such prioritisation must involve the leveraging of research funds to increase the overall pool available, so that research participants do not merely displace other eligible people.

Using this model, contraception would fit into the 'scope of entrustment' for HIV prevention trials, along with testing for and treatment of sexually transmissible infections (which is standard practice) and compensation for illness and/or disability arising from use of the experimental drug (which is what the Cambodian sex workers sought).

[67] B. Lo, N. Padian & M. Barnes. The Obligation to Provide Antiretroviral Treatment in HIV Prevention Trials, *AIDS* 2007; 21: 1229-1231.

Stobie and Slack argue that taking the principle of reciprocal justice seriously would mean that both infected and uninfected participants deserve equal contribution of thanks, suggesting that ART provision would provide an unfair benefit to those who seroconvert[68]. This account fails to recognise that while risk is theoretically borne equally by the participants in a randomised trial, its outcome – harm – is experienced asymmetrically. It is unknown who will receive the experimental agent, it is unknown whether its effects will be beneficial or detrimental and it is unknown who will be exposed, and at what level, to HIV infection while on the trial. All bear the risk, but through the confluence of a range of factors, only some experience the burden of actually acquiring HIV. Providing compensatory care for those who are 'unlucky' – those who experience reasonably predictable harms that affect some but not all individuals – is an equitable approach to off-setting the inequitable burdens.

In 2008, Macklin addresses the role of changing circumstances in creating obligation. She argues for ART provision as an act of beneficence and an exercise in justice-as-reciprocity neatly reversing 'ought implies can' to 'can implies ought'.

Millum (2009) raises a problem with the claim that the obligation is there because it is now possible, through alliances with other parties, to provide ART with relatively little burden upon researchers.[69] Millum points out that the putative obligation is upon researchers and

[68]M. Stobie & C.Slack. Treatment Needs In HIV Prevention Trials: Using Beneficence To Clarify Sponsor-Investigator Responsibilities. *Dev World Bioeth*, 10(3):150-7..doi: 10.1111/j.1471-8847.2009.00272.x

[69] J. Millum. Post-trial Access to Antiretrovirals: Who owes What to Whom? *Bioethics* 2009. doi: 10.1111/j.1467-8519.2009.01736.x. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1467-8519.2009.01736.x/full [Accessed 13 Sept 2010].

trial sponsors, not upon governments and international aid agencies, to provide ART for seroconverters in research trials. Governments and aid agencies, he contends, should have their own priorities for distribution of ART. Given that everyone who has HIV at a stage that requires treatment deserves it, and governments' obligations are to the citizenship and not to select groups thereof, Millum argues that it is not justified to shift resources from non-participants to participants (Recall that this was one of the issues in the Cameroon PrEP site – the demand for ART already outstripped supply and prioritising research participants would displace others.). Millum writes:

> The central problem with using either beneficence or justice to ground an obligation to supply ART to trial participants is that neither gives us reason to privilege trial participants over other equally needy people. Duties of beneficence and duties to rectify injustice are grounded in the unfortunate situation of the beneficiaries; they are not dependent on the beneficiaries participating in clinical trials.

The justification for special treatment of research participants rests upon reciprocity, according to Millum. Their participation in research is primarily of benefit to others, and hence they are owed 'an appropriate response to the benefits received'.[70] Millum does not conclude that this obligation is necessarily that of life-long ART (recall that for the Cambodian sex workers, insurance against any long-term adverse effects of the trial drug was the key goal), but he is adamant that if ART is provided, it ought not to be at the expense of others.

[70] Ibid: 7

Millum's contention that the obligation is not necessarily to provide access to ART is based on arguments that the strength of the obligation can vary according to individual factors within trials. Firstly, the researcher/participant relationship may be brief and superficial; secondly, the duties of reciprocation depend on the benefits generated, and that these benefits vary between trials.

The first part of Millum's argument pays too little attention to Belsky and Richardson's 'scope of entrustment',[71] which for an HIV prevention trial clearly includes treatment for the condition under study. Regarding the strength of the claim, trials may vary somewhat in their requirements of participants, but ongoing, regular monitoring over a number of years is the expected obligation of participants, which is hardly an insignificant relationship.

The second aspect of Millum's argument is grounded in a notion that only *some* HIV prevention trials provide the kinds of benefits (in terms of knowledge) that would justify ART provision as an appropriate response. While undoubtedly some trials produce generalisable knowledge that could transform the prevention of HIV, it would be a very crude analysis that rated participation in such a trial above a trial of a failed product, or a harmful product. Can Millum seriously imply that participants in the male circumcision trials which changed the landscape of HIV prevention are owed more than, say, participants in the Carraguard microbicide study, which showed safety but no efficacy? Clinical research is an

[71] Belsky & Richardson, *op cit.* note 62.

iterative process and learning progresses at each stage. Learning what does not work is as important as learning what does.

Thirdly, Millum's contention that the obligation to seroconverters on a research trial is borne by the researcher alone is flawed. The responsibility of the researcher does not nullify the pre-existing obligations of a government to its citizens, nor of the international humanitarian community to people in need. Hence a model of shared care, to which researchers contribute but are not solely responsible, is appropriate. This position is adopted by Lo and colleagues, who extend the argument to contend that ART provision should be community-wide, rather than limited to trial participants.[72] Taking the obligation to provide ART to seroconverters as a given, the basis of their argument is social justice, and they advance two reasons for this position. Firstly, in a community where a major HIV prevention trial is being conducted it is possible that there will be participants from past trials in the area for whom ART was not provided. Secondly the research project should generally aim to reduce health disparities, not increase them by constructing a new level of privilege and disadvantage.

In accordance with the obligation to provide ART in resource-poor setting, they argue that if national programs are up and running, the sponsor/researcher should contribute to these programs in a way that facilitates the sustainability of the programs. Donor money should be used in strategic ways to reduce the structural barriers to accessing treatment for communities

[72] Lo et al. *op. cit.* note 66.

(such as distance from health facilities), not just individual participants. Providing a bus service, they argue, is a better intervention than simply transporting single participants to medical appointments. This concept fits neatly with Millum's view that fulfilment of obligations to participants should maintain or increase the global provision of ART, though he disagrees that the researchers have any specific obligation to the wider population and that government and aid agencies have an obligation to research participants. It dovetails with the argument advanced by Shapiro and Benatar,[73] that there is an obligation for researchers to ratchet up infrastructure and care so as to benefit the whole population, rather than limiting benefits to research participants.

The logistical problem that arises from the argument that researchers' obligations ought not to be offset to other institutions nor be fulfilled at the expense of other needy people, is summed up by Macklin:

> The NIH and the MRC have as their mission the conduct of research, not the provision of health benefits to research subjects or the developing countries from which they are drawn. It is in ... the[ir] interest to conduct research efficiently and effectively, and that can only be done by sticking to their narrow mission.[74]

[73] K. Shapiro & S.R. Benatar. HIV Prevention Research and Global Inequality: Steps Towards Improved Standards of Care. *J Med Ethics* 2005; 31: 39–47.

[74] R. Macklin. 2004. Striving for a Single Standard. In *Double Standards in Medical Research in Developing Countries*. Cambridge, UK; Cambridge University Press: 101-102.

Given that true universal access remains a dream, it is timely for research funders to revisit their mission, and recognise that their moral obligation requires that provision of benefits to participants (or at least facilitation of, and contribution towards, benefits) be considered as legitimate an expense as the salaries of research staff, or the costs of transporting blood samples to laboratories.

Discussion

Why argue for the right for trial participants to access ART – and other necessary medical benefits, as required – when all people with HIV who require treatment have that right, grounded in human rights conventions?[75] Does this not privilege the rights of the few over that of the many? It is not, in my view, a question of placing the rights of some over others, but of articulating the responsibilities of different agencies toward different populations and individuals, with a view to creating a context that facilitates the goal of universal access.

The generalised right to health as articulated in human rights conventions, in particular the *International Covenant on Economic, Social and Cultural Rights,* places responsibilities upon governments and the international community. But other parties also bear specific responsibilities: for example, physicians have particular responsibilities to provide care for their patients, and the research community, as I have argued in the article, has a special

[75] United Nations General Assembly. *International Covenant on Economic, Social and Cultural Rights,* 16 December 1966, 993 UNTS 3 at Article 12 (entered into force 3 January 1976). Available at: http://www2.ohchr.org/english/law/cescr.htm [Accessed 3 Mar 2010]. Note that the US has never ratified this, as it appears to mandate universal access to healthcare.

responsibility towards research participants. Stressing both physician/patient responsibilities and researcher/participant responsibilities do not undermine the generalised claim for care by the needy, but they apportion that responsibility in specific ways. In my view, the delineation of responsibilities to provide care creates an enabling environment for universal access.

Consider the real-world effects of short-course AZT trials, which proved that giving less of the drug to poor women produced a result that was less effective than best practice, but better than nothing. The short-course regimen was not then implemented in southern Africa. Proving that short-course AZT was better than nothing for vertical transmission did not create momentum for significant price reductions and improved access. Those results supported the indecent pricing of the drug, by establishing a regimen that encouraged giving less drug for less effect in poor populations (resulting in more HIV positive babies), rather than fuelling arguments for reasonable, affordable drug prices for all.[76]

Putting the public health goals of a developing nation above the protection of the individual research subject, by allowing researchers to discount standards of care, places a lower value on the life of that subject, and this process supports, rather than challenges, global inequities. Access schemes created to support research projects, on the other hand, build capacity to scale up for broader provision of essential health services.

[76] While there were, and are, substantial logistical problems with providing optimal treatment and prophylaxis to pregnant HIV positive women who present late for care, the short course AZT trials focused on giving less drug to poor women, rather than exploring optimal dosing within logistical constraints. The high price of the drug was taken as given, rather than a possible variable.

Protecting the rights of the individual research participants and requiring those who have a responsibility to honour them, prevents exploitation and upholds a notion of global equity. The alternative is the perpetuation of double standards which support an assumption that inequity is inevitable (and implicitly acceptable).

Summary and conclusions

The devastation caused by HIV/AIDS in the developing world spawns two very different responses: one, which I characterise as relativist, a movement to work within the contextual constraints to research appropriate interventions; the other, universalist in scope, is an outcry against exploitation, and a desire to police the obligations that the researcher has to protect the research participant. The basic question being asked was: do research participants everywhere have the same rights? The answer to this, *a priori*, is that they do (or should).

Where the relativists and the universalists part company is on the reasoning about how to best protect the interests of those participants. The universalists argue that this means importing standards of care and post-trial care from the developed world, against which to test more context-appropriate interventions, as the protection of the individual research participant is the primary obligation of the researcher. The relativists argue that research participants are part of a community, and that community interests are best served by acknowledging the reality of local circumstance. Therefore, context-appropriate interventions should be tested against the baseline therapy currently available in the community, even if that is nothing.

While this debate raged, in the resource-rich world, the control of HIV-related diseases using combination antiretroviral therapy became the good news story of the late 1990s. The ascendancy of ART and reframing of HIV as a manageable chronic infection catalysed a struggle for equity in global health: the treatment access movement. This movement sought to displace the assumptions of unaffordability and excessive complexity, and replace it with the simple demand for equity, for recognition that access to life saving treatment had to be seen as a necessity and a right, not a privilege reserved for the affluent.

The stark disparity in access to life-saving drugs rekindled the question of what was owed to research participants in HIV prevention trials. The populations needed to test new prevention technologies were precisely those that lacked assured access to life saving treatment for those who seroconverted.

The PrEP trials discussed in this article represent a great social failure of institutionalised clinical research. These trials are important, because the views of the potential participants are brought to the fore, and they are insistent and compelling in their demands for what they consider to be reciprocal justice in research.

The experience of the PrEP trials, particularly in Cambodia, and the example of the treatment access movement, shows that people in the developing world want justice. This is to say that they want access to health care and treatment, and that they do not accept profit – even the putative future profit for humanity – being placed over their lives and well being. The

argument that researchers have a duty of care – indeed, a moral obligation – to ensure that therapy for the disease under study in prevention trials is available, is significant because it broadens the role of research in the developing world. Rather than functioning as a dislocated, disinterested machine for the production of knowledge, this obligation creates a new role for research as part of a capacity building project that can help to redress health disparities.

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Part 2, Chapter 1

Survey of principal investigators of HIV biomedical prevention trials

Publication status: This chapter is not intended for publication.

Introduction

HIV prevention research is usually conducted in populations at very high risk of HIV in order to get a timely result. Because a confluence of social, political, geographical and biological factors contribute to HIV risk, people from high risk populations are also likely to be vulnerable to exploitation (UNAIDS 2012, 10). People from these populations may also derive great benefit from getting access to effective HIV prevention technologies. Accordingly, it is well recognised that those conducting HIV prevention research are obliged to promote the rights and welfare of participants, and specifically to provide them with HIV prevention options that lower their risk rather than exploit their vulnerability to HIV acquisition (e.g. UNAIDS 2012, Rennie and Sugarman 2010, UNAIDS 2000).

Therefore, a complex package of prevention and care is negotiated for participants in HIV prevention trials. This can include effective HIV prevention interventions, sexual and reproductive health care, other medical care whether or not it is directly related to trial participation, access to antiretroviral therapy (ARV) for those who acquire HIV, and development of capacity and infrastructure within trial communities. These measures collectively constitute *the standard of care* for trial participants.

While standards of care in different trials contain common elements, implementation can vary significantly (Heise, Shapiro and West Slevin 2008). In addition, technological advances in HIV treatment and lessons learned from initial HIV prevention trials have led to expectations evolving over time different levels of care, and an increased emphasis upon community negotiation and collaboration (e.g. Page

Shafer et al. 2005; Feldblum et al. 2008, 7; Ramjee, Kamali& McCormack 2010, UNAIDS 2011).

This raises the question of what the standard of care should be for trials, whether there should be a minimum standard, and how the affected communities can have a say in the matter. This survey seeks to determine how principal investigators of HIV biomedical prevention trials approach determinations of standard of care.

Aims

This study sought to survey principal investigators who had conducted HIV biomedical prevention research between 2000 and 2011, a period in which there was significant change in terms of access to antiretrovirals in low- and middle-income countries. The aim was to assess the self-reported factors that principal investigators took into account when making decisions about standards of care for participants in HIV prevention research, as background to further in-depth interviews with a subset of participants. Specifically the survey aimed:

- To establish what forms of ethical guidance, if any, that the principal investigators based their deliberations upon;
- To determine whether principal investigators were committed to particular standards of care (including ancillary care and treatment for seroconverters);
- To see if either standards changed over time, and/or if reliance on particular forms of ethical guidance changed over time;

- To establish whether/how principal investigators facilitated capacity building in the form of community collaboration and/or development of health infrastructure; and
- To ask whether principal investigators were satisfied with the final outcome.

Methods

Eligibility

People were considered eligible for the study if, between 2000 and 2011, they had conducted a phase IIb or phase III trial of a biomedical intervention that was designed to prevent sexual transmission of HIV.

To identify the study population, I searched the Current Controlled Trials and clinical trials.gov databases for trials between 2000 and 2011 using the term 'HIV prevention' I then sorted through results to find efficacy trials of biomedical HIV prevention interventions for sexual transmission that were either phase III or IIb. Twenty-eight trials met these criteria. Principal investigators (PIs) and first authors of key publications from these trials were contacted by email and invited to participate in the study by responding to a survey.

Recruitment

Eligible PIs were contacted by email and sent information forms and a link to the questionnaire. Potential participants were also followed up in person at international conferences (Microbicides 2010 in Pittsburgh, International AIDS Society in Rome and Microbicides 2012 in Sydney) and through mediated email introductions and

recommendations provided by colleagues. Each eligible PI was sent at least one reminder email. Four ineligible responses were received and deleted. The recruitment aimed at achieving a purposive sample of PIs in which all of the prevention trial modalities were represented and key opinion leaders who had conducted more than one HIV prevention trial were included.

Study design

The questionnaire was designed using SurveyMonkey Select software. The conceptual framework was based on categories established in a seminal 'standards of care' mapping study (Heise, Shapiro and West Slevin 2008). The questionnaire was piloted online with two staff members and three students at the Centre for Values Ethics and the Law in Medicine (VELiM). The survey went live in May 2010.

Initial responses from eligible PIs highlighted some further difficulties with the questionnaire design, particularly the requirement that people repeat the questionnaire several times depending on the number of trial they had conducted. Accordingly, the study was re-designed and piloted again with two members of the ethics committee of ACON (formerly known as the AIDS Council of NSW) and two staff members from the Kirby Institute. Following feedback, further alterations were made to the format wording and the sequence of questions, and provision was made within the questionnaire to report on more than one study. Due to the difficulty of recruiting PIs, those who had responded to the initial questionnaire were not asked to complete the revised one.

The questionnaire had a multiple choice format, with specific questions allowing more than one response, and others limited to one only. In many cases, a free text field was also provided for respondents to add additional information (see Appendix D for full questionnaire and summary of responses). Respondents were asked about the first HIV prevention trial they had reviewed and then about the most recent. Descriptive statistics in the form of simple frequencies were calculated for responses to closed-ended questions, and summaries were compiled for free-text responses where they were provided.

Data collected from both the initial survey are reported alongside data collected from the revised survey. Where the questions differed slightly, this has been noted. If the difference is such that the two sets of results are not commensurate, the initial survey results are reported separately.

Data were collected from all respondents on the inclusion of male circumcision in standards of prevention. However it was not clear from these data which trials took place after the release of circumcision efficacy results in 2007. In trials that took place before 2007, there would be no expectation of including circumcision in the standard of care, but for those that took place afterward and had male uncircumcised HIV negative participants, it is an important question. Accordingly, the relevant PIs were contacted by email to provide clarification. This information is presented along with survey results.

These surveys were approved by the Human Research Ethics Committee of the University of Sydney.

Results

Final survey

Seventeen eligible respondents began the survey and 16 completed it. Five respondents had completed one trial and 12 more than one. All HIV prevention modalities except for HIV treatment-as-prevention were represented in the final survey.

Respondents were asked about their first and their most recent trial, and to provide dates where possible. Six of the dates listed for the first trial however fall outside the eligibility criteria set for this study. Entry into the survey was by invitation only, and invitations were only sent to eligible individuals. Therefore principal investigators who were eligible based on their more recent work had also worked on much earlier trials, which I had not anticipated. Rather than deleting these responses I have kept then in the analysis, which therefore gives a picture of a slightly wider time period than was originally intended (from 1994 -2011 rather than 2000-2011).

Initial survey

Ten eligible participants completed the survey. HIV prevention modalities represented were PrEP, HIV vaccines, microbicides, HIV treatment-as-prevention and the diaphragm.

HIV prevention modalities represented

When the initial survey and the final survey are combined, PIs from all of the HIV prevention modalities researched between 200 and 2012 are represented in the purposive sample.

Table 1 HIV prevention modalities represented

Survey question: Which HIV prevention modality did your prevention trial/s study?

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)		
		One trial only (n=5)	FIRST HIV prevention trial (n=10)	MOST RECENT HIV prevention trial (n=12)
PrEP	4 (40%)	1 (20%)	2 (20%)	6 (50%)
HIV vaccine	2 (20%)	0	1 (10%)	2 (17%)
Male circumcision	0	2 (40%)	0	2 (17%)
Microbicide	8 (80%)	2 (40%)	3 (30%)	1 (8%)
PrEP/microbicide (single trial)	0	0	0	1 (8%)
HIV Treatment-as-prevention	1 (10%)	0	0	0
STI Treatment-as-prevention	0	0	2 (20%)	0
Diaphragm	1 (10%)	0	2 (20%)	0

Dates of first trial

- *June 2008*
- *February 2005*
- *1994*
- *2004*
- *1999*
- *1994*
- *1996*
- *None of the above: I was involved in trial of AZT to prevent MTCT in 1995-6*
- *1995*

Dates of most recent trial

- 2005
- 2007
- 2010
- August 2009
- 2007
- February, 2002
- 2008

Initial survey

In the initial survey respondents reported names of trials rather than dates, which will not be reported for reasons of confidentiality.

Guidance questions

Each PI cited several sources of ethical guidance. The Declaration of Helsinki was the most commonly consulted document overall, with 28 respondents citing it. Both the national guidelines of the host country and the researchers' institutional guidelines increase from the first to the most recent trial, as does ICH-GCP.

Table 2. Ethical guidelines consulted by principal investigators

Survey question: 'Did you consult any ethical guidelines in designing your trial? If so, which guidelines did you consult?'

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)		
		One trial only (n=5)	FIRST HIV prevention trial (n=11)	MOST RECENT HIV prevention trial (n=11)
Declaration of Helsinki	8 (80%)	5 (100%)	7 (63%)	8 (72%)
ICH-GCP	0	4 (80%)	6 (54%)	9 (82%)
Host country national guidelines	3 (30%)	1 (20%)	6 (54%)	9 (82%)
Sponsoring country national guidelines	0	2 (40%)	6 (54%)	0
Researcher's institution national guidelines	0	2 (40%)	6 (54%)	9 (82%)
US federal regulations (the Common Rule)	1 (10%)	2 (40%)	6 (54%)	8 (72%)
CIOMS	3 (30%)	1 (20%)	3 (27%)	3 (27%)
UNAIDS	3 (30%0	1 (20%)	4 (36%)	7 (64%)
Nuffield Council on Bioethics	1 (10%)	0	1 (9%)	0
HPTN	1 (10%)	0	3 (27%)	5 (45%)

Additional guidance cited:

- *MRC Guidance on Provision of ART in developing countries May 2003 (I trial only)*
- *Read numerous issues of the Hastings Institute's "IRB: Ethics and Human Research" (I trial only)*
- *Regularly read Hastings Institute "IRB: Ethics and Human Research." (most recent trial)*
- *Collaborative Institutional Training Initiative (CITI) (initial survey)*

Where was ethics approval obtained?

Ethics approval was obtained from multiple sources by all PIs. All PIs in the initial survey, and those who had conducted one trial only, reported obtaining ethical review in the trial's host country. Most, but not all PIs who conducted multiple trials also reported this (10/12 for the first trial, 11/12 for the most recent).

Table 3. Where was ethics approval obtained?

Survey question: 'Where did you obtain ethical review?'

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)		
		One trial only (n=5)	FIRST HIV prevention trial (n=12)	MOST RECENT HIV prevention trial (n=12)
Host country	10 (100%)	5 (100%)	10 (83%)	11 (92%)
Sponsoring country	9 (90%)	4 (80%)	7 (58%)	8 (67%)
Country of researcher's academic institution	0	2 (40%)	11 (92%)	10 (83%)

Most recent trial

Respondents from both the final and the initial surveys supplied a list of ethics committees who reviewed the HIV prevention trials. Forty-one distinct ethics committee were named. Six respondents provided only general information, such as ‘plus each group with whom we collaborated for trial implementation’ ‘multiple African IRBs’, ‘plus two UK ethics committees; and ‘too many to list’. (For further information on how this list was used, see Pt 2 Chapter 2.)

Standard of Prevention/risk reduction package (including contraception)

Respondents were asked which particular components in the HIV risk reduction package offered to all participants (‘standard of prevention’).

All respondents in both the final and the initial survey reported that male condoms were supplied, and all final survey respondents also provided counselling (respondents in the initial survey were not asked about counselling). There was less unanimity with other prevention options. Treatment for sexually transmissible infections (STI) was offered by all but one respondent (most recent trial), and testing for STI was offered in all but two instances (most recent trial and first trial – same respondent – STI treatment was available on the basis of symptoms, known as ‘syndromic management’). As Table 4 shows, there was considerable variation regarding provision of contraceptive options, cervical screening and treatment, male circumcision and other preventive medical services. Of note, some trials enrolled men only and some women only, so all options were not applicable to all respondents.

Table 4. Health/prevention services offer to trial participants

Survey question: 'Which health/prevention services did the trial offer participants?'

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)		
		One trial only (n=5)	First trial (n=12)	Most recent trial (n=12)
Counselling	n/a	5 (100%)	12 (100%)	12 (100%)
Male condoms	10* (100%)	5 (100%)	12 (100%)	12 (100%)
STI treatment	10† (100%)	5 (100%)	12 (100%)	11 (92%)
STI testing	10† (100%)	4 (80%)	10 (83%)	11 (92%)
Oral contraceptive pill	4‡ (40%)	2 (40%)	6 (50%)	7 (58%)
Injectable contraception	4‡ (40%)	2 (40%)	4 (33%)	7 (58%)
Male circumcision for partners/participants	0	2 (40%)	1	4 (33%)
Female condoms	5* (50%)	1 (20%)	5 (41%)	8 (66%)
Contraceptive implants	3‡ (30%)	1 (20%)	0	0
Cervical screening	7 (70%)	1 (20%)	6 (50%)	7 (58%)
Treatment of cervical dysplasia	3 (30%)	0	0	2 (17%)
Hepatitis B vaccination	1 (10%)	1 (20%)	2 (17%)	5 (41%)
Referral to local services for non-trial related conditions	8 (80%)	0	10 (83%)	12 (100%)

Notes on differences between the initial survey and main survey:

Respondents were not asked about counselling.

*Male condoms supply was divided into 'free and unlimited access' (9) and 'limited number' (1). Female condoms use was also divided into 'free and unlimited access' (4) and 'limited number' (1).

† STI testing and treatment were treated as a single question.

‡Hormonal contraceptives were categorised as 'limited options' (1) and 'comprehensive options' (3).

Comments

- *Female condoms not offered only because the trial was a diaphragm trial and their use together was contraindicated*
- *Female condoms were hardly available; MC was not proven to be effective yet; cervical screening was done where feasible with referral for care*
- *We talk about male circumcision but since we work with women only, do not offer it for their partners. We refer for cervical dysplasia*
- *The number of condoms was locally determined; referral for treatment of cervical dysplasia if locally available, cervical screening was only done if local referral was possible.*
- *This arrangement is made through PEPFAR programs in the country*
- *Research clinics in primary health care location and therefore all primary health care services provided to participants by research staff, with reporting via local clinic*
- *[Contraceptive] implants were not universally available, and cervical screening was only available in South Africa where there is a national programme*
- *There were no women enrolled in the study*

Addition information about male circumcision as 'standard of prevention'*

Four trials in this sample enrolled HIV negative heterosexual men after the release of efficacy data on circumcision. Phambili (HIV vaccine trial) provided proactive access (before national or international guidelines were released). TDF-2 (PrEP trial) provided information once the official recommendations from the government were released. HPTN052 (Treatment-as-prevention) did not inform participants in a formal and systematic way regarding the results of the circumcision studies because this was not a procedure that was being offered at most of the local settings in which study sites were located. Partners PrEP sites informed relevant participants (HIV- uncircumcised men) and provided active referral (checking in on whether successfully taken up, etc.) for interested

men. Additional scope of activities in Partners PrEP sites varied by site – some sites had circumcision programs as part of their other funded activities.

**Specific information obtained by emailing respective PIs or senior staff.*

Other ancillary care

Respondents were asked whether their committees required particular elements to be available as ancillary care for trial participants, and most offered some level of care, limited either by site capacity alone or to conditions that might impact on trial findings. Only two respondents overall reported no ancillary care was available (from the initial survey).

Table 5. Ancillary care

Survey question: **'**Did your trial proposals offer other medical or prevention services to participants (such as treatment for common illnesses)?'

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)		
		One trial only (n=5)	FIRST HIV prevention trial (n=11)	MOST RECENT HIV prevention trial? (n=12)
Yes limited to conditions that might impact the research findings	3* (30%)	2 (40%)	6 (54%)	5 (42%)
Unlimited, except by site capacity	4† (40%)	3 (60%)	4 (36%)	5 (42%)
No	2 (20%)	0	0	0
Yes, to treat conditions associated with HIV (such as TB, cervical cancer)	1‡ (10%)	0	1 (9%)	2 (17%)

Phrasing of questions for initial survey was slightly different:

* Sufficient to ensure the smooth running of the research

†To treat conditions uncovered by the research process

‡To the degree possible on the basis on need.

Comments:

- *In practice, care was unlimited for participants that presented to the research clinics with problems, although none of the centres could admit to hospital*
- *This question cannot be accurately answered as it is worded. As I indicated, we offered a full range of HIV prevention services which had been proven to work at that time, and we offered mass STI treatment in the intervention arm. For ethical reasons, we referred symptomatic control arm persons to government clinics.*
- *Physical and medical examination and as well as providing all the known bio-medical prevention tools available on the site eg condoms, risk reduction counselling, STI treatment etc.*
- *Regarding the previous question, the trial enrolled only young HIV-negative men, so many of the services asked about were not applicable.*

Benefits for families/partners

Most respondents reported that trial related benefits were not available to partners or families of participants, though services to partners and families increased for the most recent trial. The main partner/family services detailed were STI treatment, HIV testing and counselling and condoms.

Table 6 Benefits for families/partners

Survey question: **'**Did your committee require benefits to be provided to partners of families of participants?'

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)		
		One trial (n=5)	FIRST HIV prevention trial (n=12)	Most recent HIV prevention (n=12)
No	5 (50%)	3 (60%)	7 (59%)	5 (41%)
Yes	3 (30%)	2 (40%)	5 (41%)	7 (59%)

Comments (1 trial only)

- *This varied between centres, but in one centre the trial was enrolling serodiscordant couples, and in another running a VCT service for the community*
- *Limited to treatment of STIs*

First trial

- *Not formally (not allowed by NIH rules) but informal care was provided by many Centers*
- *Partners could get counselling, VCT and condoms*

Most recent trial

- *As above informal care was offered on a site by site basis*

Initial survey

- *HIV VCT and treatment for curable STIs*
- *Partners were able to come to the clinics for HIV testing and counseling and for STI - also locally dependent.*
- *This research specifically works with discordant couples so the partner benefits from health education and access to services provided by other donor funded activities*
- *Services available to partners and children*

Access to ARV for seroconverters

Of the ten respondents in the initial survey, two reported that ARV access was not available to seroconverters and eight reported that it was (though different means, as detailed in the table below). In the final survey, six reported that ARV access was not supplied, in the first trial and two reported they were not sure in the first trial. For the most recent trial, however, all respondent reported ARV access with the most common provider being government programs (8), an equal number provided directly through research programs and non-government organisations respectively (4), and three reporting access through international donors. Many respondents also provided more detailed comments about implementation of ARV access, listed below in Table 7.

Table 7. ARV access for seroconverters

Survey question: Was antiretroviral therapy (ARV) provided to participants who seroconverted during the trial?

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)		
		One trial only (n=5)	FIRST HIV prevention trial (n=12)	MOST RECENT HIV prevention trial (n=12)
Yes, through government programs.	4 (40%)	2 (40%)	5 (42%)	8 (66%)
Yes, through NGO programs	0	1 (20%)	1 (8%)	4 (33%)
Yes, through international donor programs	1 (10%)	2 (40%)	1 (8%)	3 (25%)
Yes, directly linked to the research program	1 (10%)	0	1 (8%)	4 (33%)
Not sure	0	0	2 (17%)	0
No	2 (20%)	0	6 (50%)	0

Comments (I trial)

- *3 centres referring into trial that provided immediate ART for 2 randomisation groups*
- *Seroconvertors were initially accompanied to ART services at the host institutions.*

First trial

- *Encouraged the participants to join other studies [such as] the START trial, depending on their CD4 count results.*
- *Participants were referred to local HIV treatment centers and managed according to local standards of practice. Who paid for the drugs would vary by country and site.*
- *We are part of the local health department and were able to provide linkage to clinics that provide ARVs.*
- *Combination ART was not even proven to work until the trial was almost finished, and as noted in my prior answer, our donors (NIH, Gates,) specifically prohibit us from buying ART with their money, and until PEPFAR came to Uganda in 2004, we had NO access to ART. Again, this was not a decision made by the research team.*
- *Antiretrovirals were not available when we did our first microbicide efficacy trial in the 1990s*
- *The intervention itself was AZT, which is an antiretroviral. However, the trial occurred before ARVs were widely available. After the trial was over, the participants had priority to obtain ARVs.*

Most recent trial

- *All sites participating in our most recent study have to have a pathway for referring all participants who seroconvert. Depending on the stage of infection (usually early) they may or may not need immediate treatment. If they need treatment it might be provided through local resources or through agencies / programs such as PEPFAR.*
- *We provide ARVs to trial participants and their communities through a PEPFAR program*

- *We created a post-test support group, provided free care for opportunistic infections, and linked positives to care and treatment facilities*
- *Initial survey*
- *At the start of the MIRA study in 2003, nothing was really in place. By the end of the study each site had a plan to link seroconverters to care. In Durban and Harare, participants were linked to government programs. In Jo'burg, the same, although I think the ARV clinic was a direct PEPFAR clinic, if that is what you mean by "international donors". The study assisted the participants in enrolling into national programs by providing transport, CD4 results, etc. and in some cases escorting people to the ARV clinics to assist them in navigating the process*
- *At the time of COL-1492, ARV was not widely available yet.*
- *We refer participants to existing facilities and that can be government or international. You should allow these two options to be checked.*
- *Last three options - most women were referred, funds were made available to help with the care of seroconverters.*
- *ARV access to volunteers who test positive. Seroconverters are referred to an acute infection study initially and transition to the treatment program when eligible based on local treatment guidelines*
- *Available through PEPFAR funding to the host research institution and implemented in partnership with the government program who provide all drugs. Very integrated to the research process and available in clinics next door to the study clinics.*

Access to ARV for the screened out

Incomplete data only are available on respondents' reports of ARV access for people who volunteered to participate, but were ineligible due to pre-existing, hitherto unknown, HIV infection. Due to an error in the survey, this question was not asked for the most recent trial. Eleven of the total number of participants asked this question reported that access was not available to this group (50%). Only two respondents said

this access was directly linked to the research program, the rest were through other government, donor or non-government sources.

Table 8. ARV access for the screened-out*

Survey question: 'Was ARV provided to volunteers found HIV positive at screening and therefore ineligible?'

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)	
		One trial only (n=5)	FIRST HIV prevention trial (n=12)
Yes, through government programs.	3 (30%)	2 (40%)	4 (33%)
Yes, through NGO programs	0	1 (20%)	1 (8%)
Yes, through international donor programs	2 (20%)	2 (40%)	1 (8%)
Yes, directly linked to the research program	1 (10%)	0	1 (8%)
Not sure	0	0	0
No	3 (30%)	0	8 (66%)

Comments

- *The uptake of referral to care providers that could provide access to ART was disappointingly low, particularly for those that were screened out because of being HIV positive*
- *I think there were studies going on in some centres that those positive at screening were referred to.*
- *Women were referred to existing programs*
- *CD4 equal to or less than 200 or clinical AIDS*
- *During the pilot study in 2005 the ART program was initiated. In discussion with the program there was concern that the study would identify high*

numbers of women in need of treatment (in feasibility study 50% of volunteers had been positive at screening). Consequently hospital asked the research team to provide CD4 tests and refer in priority order so as not to overwhelm the new service - this was funded by our sponsor and maintained throughout the trial

- *Due to a programming error, data are not available for the screened-out on most recent trials.*

Community consultation/collaboration

Community consultation throughout the research project was reported by two respondents who had conducted a single HIV prevention trial. Consultation in the planning stages only was reported by six respondents in the first trial and four in their most recent. Consultation during both planning and recruitment phases was the most popular response for the most recent trial, with nine reporting this. Five respondents reported no consultation; of these, three had conducted a single trial, one report was for a first trial and one was from the initial survey, where the timing of the trial is not clear from the data and the question was somewhat different, as is detailed below in Table 9.

Table 9. Community consultation

Survey question: 'Did you consult with communities affected by the trial about the care/prevention services that would be provided within the trial?'

	INITIAL SURVEY (n=10)	REVISED SURVEY (n=17)		
		One trial (n=5)	First trial (n=11)	Most recent (n=11)
Yes, throughout the research project	0	2 (40%)	0	0
Yes, in planning stages	2 (40%)	0	6 (54%)	4 (36%)
No	1 (20%)	3 (60%)	1 (9%)	0
Yes, in recruitment stages	2 (40%)	0	2 (18%)	3 (27%)
Yes, in planning and recruitment stages	5 (100%)	0	4 (36%)	9 (81%)
During the trial	0	0	0	10 (91%)

Initial survey (n=10) * question was worded differently: Did you discuss the distribution of research benefits with local communities?

Comments from initial survey

- *This was also an ongoing dialogue with trial participants during interviews and focus group discussions, as well as with community advisory groups.*

Comments from final survey

One trial

- *The negotiation was undertaken by the PIs of each clinical research centre, so not by me.*

First trial

- *"Care" is a rather vague term*

- *I came on board the study after the initial planning so I'm not entirely sure about this question.*
- *We provided everything that was proven at that time: health ed, condoms, HIV testing and counseling, phased in p-MTCT as the data accrued on how to do it in rural areas. The RCTs on combination ART were not completed until towards the end of our study, so they were not yet standard of care; in any case, our donors do not allow us to buy ARTs with our grants. We informed community leaders of what we could offer, but there was not much we could negotiate! It is often assumed that the researchers make the decisions as to what to offer, but in many cases, our hands are tied.*

Infrastructure

Most respondents reported that their research contributed to in-country infrastructure.

Table 10 Contribution to infrastructure

Survey question: Did your prevention trial contribute infrastructure to the host country, e.g. the training of health care workers, establishment of clinical facilities?

	INITIAL SURVEY (n=9)	REVISED SURVEY (n=17)		
		One trial only (n=5)	FIRST HIV prevention trial (n=12)	MOST RECENT HIV prevention trial (n=12)
Yes	7	5 (100%)	10 (83%)	10 (83%)
No	2	0	2 (17%)	2 (17%)

Details of infrastructure

One trial only

- *This was not the case in all centres*
- *A fully equipped clinic and laboratory, renovation of an additional clinic and provision of some equipment.*
- *Training; data management infrastructure; laboratory equipment; laboratory renovation*
- *Establishment/maintenance of clinical facilities and training of research staff*

- *Male circumcision center*

First trial

- *In addition to training project staff, there was considerable building of clinic and research facilities and local clinics were given assistance with medical supplies.*
- *Training of staff as required by protocol. research centre development(infrastructure)*
- *Training, renovations, new clinical and laboratory resources, and much more.*
- *Enhanced facilities' human and physical resources*

Most recent trial

- *MSM Training manual was produced by the site and is in the proposal stage of being involved in the health professionals' curriculum.*
- *Training of health care workers*
- *training of health workers, establishment of clinical and laboratory facilities, community education and training of community health workers*
- *Training of staff, clinical and lab buildings.*
- *Training, infrastructure development*
- *Training of surgical teams, counselors, establishment of surgical facilities, improved lab infrastructure*

Initial survey

- *Built a clinic in Cotonou.*
- *Lab and clinical infrastructure*
- *Laboratory equipment, vehicle, motorcycles, office equipment and furniture.*
- *We renovated clinics and labs.*

- *The CAPRISA Vulindlela Clinical Research and Ethekwini sites work closely with the local primary care clinics and in addition to physical infrastructure in close proximity they provide services that are not available at the PHC clinic such as ARV treatment services; patients can access other care and services not otherwise available at the PHC clinic. Staff training and support, new information sharing and technical assistance is provided to staff at the PHC clinics.*
- *lab equipments colposcopy and clinic setup*
- *Porta cabins purchased for the study mostly transferred to HIV program. Plus assisted primary health care clinics over the years with building repairs and changes to their infrastructure*

Respondents to the initial survey were asked an extra question regarding infrastructure: will this infrastructure contribute to meeting health needs or research capacity of the community post-trial?: yes (seven); no (two).

Comments:

- *if the local people pick it up*
- *if the local people choose so*
- *Laboratory equipment are useful for research*
- *if the local people continue*
- *Infrastructure and services are in place permanently and not linked specifically to this/a trial*
- *lab equipments can continue to be functional*

Sponsor policies: did the sponsor have policies that impacted on the health and prevention services offered to participants?

Most respondent reported that trial sponsors had policies that affected provision of health and prevention services to participants (two for one trial only, ninefor the first trial and ten for the most recent).

Table 11 Sponsor policies

Survey question: 'Did the trial sponsor have policies regarding health/prevention services that were made available to participants'

	REVISED SURVEY (n=17)		
	One trial (n=4)	FIRST HIV prevention trial (n=11)	MOST RECENT HIV (n=12)
Yes	2 (50%)	9 (82%)	10 (83%)
No	2 (50%)	2 (18%)	2 (17%)

The initial survey asked a different question: did the sponsor limit benefits that are made available to participants? Four respondents said yes to this, three said no, with the following comments:

- *As long as benefits are not coercion*
- *PIs [in this study] are not foreigners and infrastructure and services are in place through diverse funding sources and not just through the specific trial being discussed in this survey.*
- *Sponsor responded positively to all requests made by community stakeholders - including funding for CD4 tests and cervical cancer screening.*

How did sponsor policies impact on care?

Only one respondent indicated that sponsor policies had had a negative impact on care, while nine reported a positive impact for both the first and most recent trial. Three respondents reported that their sponsors did not have policies – one who had completed a single trial, one for the first trial and one for the most recent trial.

Table 12. Sponsor policies

Survey question: 'How did sponsor policies affect the care/prevention services offered to participants?'

	REVISED SURVEY		
	One trial (n=4)	FIRST HIV prevention trial (n=10)	MOST RECENT HIV (n=10)
Positively	2 (50%)	9 (90%)	9 (90%)
Negatively	1 (25%)	0	0
Sponsors did not have policies	1 (25%)	1 (10%)	1 (10%)

Comments

One trial

- *MRC policy for provision of ART was very helpful as it allowed flexibility which meant that PIs were able to provide as much as feasible within their setting. A strict uniform policy would probably have reduced the care to the minimum feasible*

First trial

- *Neither increase nor decrease*
- *The whole field moved several quantums (sic) in the provision of trial services/follow up...*

Satisfaction

Only one trial: *5/5*

- *Slightly concerned (as was our Trial Steering Committee) that the benefits and services provided to participants were too out of sync with what was available in reality*

First trial: *7 yes, 5 partially*

- *I do not know how provision of services was monitored nor what standard was truly required by the sites.*
- *in those days, care for AIDS patients were very limited in and outside of the trial*
- *In retrospect, more services could have been provided, but for that time (mid-1990's) the services were much more than was standard at the time.*
- *At the time, the trial was ahead of the ethical bell-shaped curve; in retrospect, it was behind as standards evolved*

Initial survey satisfaction: Six respondents said yes they were satisfied, while two said they were partially so.

Comments:

- *However[respondent had indicated full satisfaction], I feel we still could have done more to attract male partners to the clinics as although services were available for them the uptake was very low*

Discussion

The results of this questionnaire illustrate the move toward increased ARV access for participant seroconverters, with the progression from half the surveyed PIs making no provision for ARV access for their first trial to all making provision in their most recent. This demonstrates how ARV access for seroconverters has become a norm

over time. The finding is not surprising, however, as the phenomenon of increased access to ARV in low- and middle-income countries is well-documented (Macklin 2006), and this removed barriers that PIs would formerly have faced to securing access.

Several of the comments however indicated that while policies were in place, there was a degree of concern or at least nervousness as to how effective implementation of ARV access was in practice, with people referred for ARV access not necessarily getting it. Monitoring of implementation of ARV access was also a concern, as was 'overwhelming' ARV service providers with newly diagnosed HIV infections as a result of screening volunteers for prevention studies Researchers who were based permanently in the countries in which their research took place did not report these concerns, probably because they were already integrated into service networks or had the capacity to provide ARV within their research sites.

A more surprising finding is the majority perception that sponsor policies affected provision of prevention and or care services positively rather than negatively. Previous work of standards of care in HIV prevention research showed how policies such as those of the United States' National Institutes of Health (NIH) vetoed spending grant money from this source both non-trial related care and the building of permanent infrastructure, such as clinics or even significant renovation of existing facilities without specific permission. With the majority of studies (though not all) having significant funding from the NIH, it is surprising to see that a positive impact is reported by respondents. This may be due to some level of diversification of funding sources, with funders other than the NIH providing sponsorship for certain

aspects of the trial. It is possible that some respondents interpreted the question as being specifically about standard of prevention, in which case there is no barrier to the provision of condoms and STI-based HIV prevention services in NIH policy. One respondent did however provide the anticipated response, which emphasised that the donor requirement did not sit well with this particular research team:

> *Our donors (NIH, Gates,) specifically prohibit us from buying ART with their money, and until PEPFAR came to Uganda in 2004, we had NO access to ART. Again, this was not a decision made by the research team.*

Community consultation

The length and depth of community consultation appeared to increase over time, with more investigators reporting consultation during design, recruitment and throughout the trial for their most recent research compared with the first trial.

There are a number of factors that probably contributed firstly to low rates of community involvement prior to trial recruitment, and to the increased attention to community involvement in later trials. Firstly, at grant-writing stage, researchers frequently plan their research for a high risk population generally, but the specific population is determined later in the process (McCormack 2012), which can impede early community participation work. Whether or not community involvement is adequately funded is also an issue. Following the closure of the PrEP trials in the early 2000s, however, there was increasing international emphasis on community preparedness work, including the development of UNAIDS/AVAC Good Participatory Guidelines for biomedical HIV prevention trials, first published in 2007. The publicity surrounding the development and publication of this document

foregrounded the need for adequately funded community involvement, so it would be reasonable to expect an increase in earlier community involvement from this time onwards. This is not surprising, given the emphasis of community consultation in the Good Participatory Practice Guidelines (UNAIDS 2011) and also the HPTN guidance (Rennie and Sugarman 2009).

Ethical guidance

Investigators reported seeking ethical guidance from a range of sources, and each cited more than one. The choice of guidelines is likely to reflect compliance requirements of the various institutions involved, which shifted somewhat over time. The low rate of citation of the UNAIDS guidance is likely to be because this was not a national or institutional requirement. The guidelines of the host country, the researcher's institution, the US Common Rule and ICH-GCP became increasingly popular, but overall the Declaration of Helsinki was the most cited form of guidance. Investigators reported seeking ethics approval from multiple sources, nearly always including the host country and then at least one of the investigators' institution and/or another committee from the sponsoring country.

The normative question of whether investigators should aim for best practice, local standards or something in between, is touched on in several responses. One investigator reports providing 'everything proven at the time' while another has a concern *that the benefits and services provided to participants were too out of sync with what was available in reality.* 'Reality' in this quote presumably refers to the local standard in the absence of a major research project. This concern echoes an issue raised in a *Lancet* review article, that suggested that high standards of prevention in

HIV prevention research were potentially masking the efficacy of modestly effective experimental products (Padian 2008). Another quote concerning ancillary care refers to flexibility within institutional guidelines that allow *as much as feasible within their setting. A strict uniform policy would probably have reduced the care to the minimum feasible.* This comment speaks to the importance of context even within a paradigm that strives for best practice, implicitly arguing that variations between trial sites can be acceptable if that maximises care provision.

The uneven introduction of voluntary medical male circumcision in trials commencing after 2007 that enrolled eligible participants[1] is noteworthy. The use of national guidelines to determine eligibility means that in countries that were slow to include circumcision in national guidelines, eligible participants were not offered a proven beneficial intervention.

Limitations

This research has several limitations. Most obviously it comprises two surveys that are not identical, and there are some inconsistencies in language within surveys. The initial survey does not capture differences over time, while the final survey does so only crudely, as one respondent's 'most recent'; trial may be contemporaneous with another's first trial. In addition, as noted earlier, many of the first trials fall outside of the eligibility criteria, so may not be precisely comparable with the most recent trials.

[1] HIV negative uncircumcised heterosexual men living in countries with generalised epidemics

The survey was designed and went ‘live’ prior to the positive efficacy findings of new HIV biomedical prevention from July 2010, so it does not address issues of how standards might evolve in the light of new evidence.

Conclusion

Not withstanding the limitations of this section, the results of this survey suggest that there is significant variation in the ways that standards of prevention and care are conceived, designed and implemented, despite considerable attention given to normative ethics guidance. It also suggests that the ARV access movement has had a decisive impact on the care made available to both seroconverters from trials and, to a lesser extent, volunteers screened out due to pre-existing HIV infection.

The failure to introduce voluntary medical male circumcision in some sites due to slow uptake in national guidelines shows how the use of host country standards (as distinct for best practice standards) can deny participants access to a proven effective intervention in particular settings, introducing a specific difference between trial participants in the same trial who come from different countries.

References

Heise, L., K. Shapiro and K. West Slevin. 2008. Mapping the Standards of Care at Microbicide Clinical Trial Sites. Washington DC: Global Campaign for Microbicides.

McCormack, S. Perspectives of a clinical researcher at the stage of grant writing. Standards of care in Future Microbicides Research Symposium. Presentation at the M2012 symposium. Microbicide 2012, Sydney, Australia. April 15th to 19th, 2012

Macklin, R. 2006. Changing the Presumption: Providing ART to Vaccine Research Participants, *American Journal of Bioethics* 6(1): 1 - 5.

Feldblum, P. J., A. Adeiga, R. Bakare, et al. 2008. SAVVY Vaginal Gel (C31G) for Prevention of HIV Infection: A Randomized Controlled Trial in Nigeria. *PLoS ONE* 3(1):e1474.

Padian, N. S., A.Buvé, J. Balkus, D. Serwadda, and W. Cates Jr. 2008. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. *Lancet* 372 (9638):585-599.

Page-Shafer, K., V. Saphonn, L. P. Sun, M.C. Vun, D.A. Cooper, and J. M. Kaldor. 2005. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. *Lancet* 366 (9495):1499-1503.

Ramjee G., A. Kamali, S. McCormack. 2010. The last decade of microbicide clinical trials in Africa: from hypothesis to facts. *AIDS* Suppl 4:S40-9.

Rennie, S., and J. Sugarman. 2010. Developing ethics guidance for HIV prevention research: the HIV Prevention Trials Network approach. *Journal of Medical Ethics* 36(2): 810-815.

UNAIDS. 2000. Ethical considerations in HIV preventive vaccine research. Joint United Nations Programme on HIV/AIDS.

UNAIDS/ World Health Organization (WHO). 2012 (English original 2007, additional guidance point added 2012).UNAIDS／07.28E／JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS／WHO Guidance Document. Geneva: UNAIDS and World Health Organization. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf [Accessed 18 Feb 2013].

UNAIDS. 2011. Good participatory practice guidelines for biomedical HIV prevention trials. In *Guidelines for biomedical HIV prevention trials 2011*: Joint United Nations Programme on HIV/AIDS. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf.

Part 2, Chapter 2

Ethics of medical care and clinical research: A qualitative study of principal investigators in biomedical HIV prevention research

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Key words: HIV prevention, Qualitative, Ethics, Ancillary care, Duty of care

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Abstract

In clinical research there is a tension between the role of a doctor, who must serve the best interests of the patient, and the role of the researcher, who must produce knowledge that may not have any immediate benefits for the research participant. This tension is exacerbated in HIV research in low and middle income countries, which frequently uncovers co-morbidities other than the condition under study. Some bioethicists argue that as the goals of medicine and those of research are distinct, it is a mistake for researchers to assume therapeutic responsibilities while engaging in research. Others propose that there is a duty of care, but disagree as to how this is limited and specified. In this qualitative study, principal investigators from HIV prevention trials discuss their experience of providing medical benefits to participants within the context of conducting research into HIV biomedical prevention technologies. They describe the limitations imposed at times by funders and at times by infrastructure constraints, and canvass the importance of ancillary care provision and capacity building in trial communities. The views of the principal investigators are compatible with the perspective that there is a duty of care, limited by the nature of the research, the depth of the relationship between research and participant, and the capacity of the research site. The therapeutic orientation in HIV prevention trials appears to be indivisible from competent research practice by making concrete and appropriate benefits available to trial participants and their communities that support rather than compete with local infrastructure.

Introduction

In clinical research there is a tension between the role of a doctor, who must serve the best interests of the patient, and the role of the researcher, who must produce knowledge that may not have any immediate benefits for the research participant. [1, 2] This tension is exacerbated in HIV research in low and middle income countries, which frequently uncovers co-morbidities other than the condition under study. Local healthcare resources may be unable to meet these needs, so researchers have to determine the extent to which the research site should provide ancillary care (care not directly related to trial participation) to trial participants.[3]

This article explores the doctor/researcher role in the context of HIV biomedical prevention efficacy trials. It examines researchers' perceptions of their obligations to trial participants and their reflections on their experience of the doctor/researcher conflict, which may exist regardless of whether the researcher is actually medically trained. It considers these perceptions and experiences in the light of normative theoretical models that aim to define and determine the scope of the doctor/researcher's responsibility to participants, with a focus on the provision of ancillary care.

Theoretical positions of ancillary care span the gamut of positions on researcher responsibility, from the fiduciary view which considers the well being of the participant to be the primary responsibility of the researcher [4] to the non-exploitation approach, which limits researcher responsibility to implementing the protocol.[5]

Within this range two nuanced models recognise that a responsibility exists, but that it needs both to be limited and specified. The partial entrustment model delineates the scope of responsibility according to the connection between the condition under study and the co-morbidity, together with the strength of the claim, assessed largely by participant vulnerability and the potential impact of non-treatment.[3] The capacity-based model considers the urgency of the need, the strength of local healthcare infrastructure and the scope of the research infrastructure.[6] I will argue that the partial entrustment and the capacity-based models can be combined to provide a useful account of how to address relevant medical needs within the capabilities of the research project.

Background

The doctor/researcher role has an interesting history in HIV research. In the early days of the epidemic when HIV infection was synonymous with illness and death, activists argued that “a drug trial is health care too”, [7] and transformed regulatory systems to get better access to experimental treatment .[8, 9] With the advent of effective antiretroviral treatment in 1996, attention turned to HIV prevention research, which is qualitatively different to treatment research, insofar as participants in prevention trials are not ‘patients’, but are people at high risk of acquiring HIV.

Prevention research did not produce effective products for more than a decade, and various strategies were explored including, treatment-as-prevention, pre-exposure prophylaxis (PrEP), circumcision, vaccines, the diaphragm and microbicides.[i][10]

Microbicides are topical agents designed to prevent HIV infection through vaginal exposure.[ii] The first of these, nonoxynol-9, paradoxically increased participants' risk of HIV acquisition.[11] Nonoxynol-9 was followed by five subsequent microbicide products that all failed to protect against HIV, two of which arguably increased HIV risk, albeit at non-statistically significant levels.[12, 13] To date, the sole partially effective microbicide product is tenofovir gel, found to reduce HIV acquisition by 39 percent in 2010, a result awaiting confirmation.[14]
Another female-controlled approach, the diaphragm showed no protective benefit.[15]

Of four vaccine trials conducted, only one produced a marginally positive effect and another appeared to increase risk in a sub-population.[10,16]

Circumcision[iii] was the first biomedical prevention breakthrough, with three trials showing it reduces HIV acquisition in heterosexual men in HIV endemic areas by about 50 percent.[17, 18, 19]

[i] This research does not include biomedical prevention of vertical (parent-to-child) HIV transmission as the issues are significantly different, given that incidence of vertical transmission is predominantly about the failure to implement universally accessible programs successfully in high incidence regions.

[ii] Rectal microbicides are also being developed to protect women and men who have receptive anal sex.

[iii] I am not adopting the term 'medical male circumcision' because of activist critiques that claim this terminology implicitly legitimises the notion of a 'female' circumcision.

Daily use of antiretroviral drugs for HIV prevention (pre-exposure prophylaxis or PrEP), reduced HIV acquisition by 44 percent in iPrEx,[20] with two subsequent trial results showing higher risk reduction of 62 percent[21] and 75 percent [22] respectively. Prior to iPrEX, however, three of four trials testing PrEP had been shut down prematurely due to community concerns.[23]

Treatment-as prevention strategies were initially focused on treating sexually transmissible infections (STIs) understood to facilitate HIV infection, with mixed results.[16] In 2011, however, early treatment of HIV with antiretroviral drugs (ARV) reduced the acquisition of HIV by sexual partners by 96 percent, a ground breaking result.[24]

Many of the same HIV prevention researchers were involved in successive trials of products that were unsuccessful. How this experience affected subsequent decisions regarding the negotiation of participant benefits in HIV prevention trials is important for understanding the researchers' self-perception and the doctor/researcher role. In addition, rapid scale up of HIV treatment services occurred in countries that hosted HIV prevention trials during the period spanned by this research, which had considerable impact on the levels of care that were considered feasible and coloured perceptions of what care ought to be available.[iv]

Methods

Twenty-eight efficacy trials of biomedical HIV prevention (either phase III or IIb) were identified between 2000 and 2011 through the Current Controlled Trials and

[iv] Thanks to an anonymous reviewer for pointing out the importance of this contextual element

clinical trials.gov databases. Principal investigators and first authors of key publications were contacted by email and invited to participate in the study by participating in a semi-structured interview.

A purposive sample of 14 principal investigators from the 28 trials identified were interviewed, who between them had worked on more than 20 HIV prevention trials[v]. Both men and women were included in the sample. Of the principal investigators interviewed, two were 'in-country' investigators, meaning that they headed the study at a particular trial site, but did not have oversight of the trial as a whole. The remaining 12 informants oversaw whole trials and in some cases networks of HIV prevention trials. Most of these informants had been a principal investigator or a senior member of the research team on more than one study. Eight of the informants were doctor/researchers (informant numbers 1-8) and six were public health experts (informant numbers 9-14).

All of the interviews were conducted by the author. Nine interviews were conducted by telephone and five were face-to-face. The study was reviewed and approved by the ethics committee of the University of Sydney. Informants were asked 'Have you, or others in your research team, experienced tensions or conflict in the role as a doctor and role as a researcher in HIV biomedical prevention trials in developing country

[v] None of the interviewees had led a circumcision trial, but all other horizontal biomedical prevention modalities were represented in the sample.

settings?(Prompts: details of incidents, broad tensions?)'[vi] Data was coded using N-Vivo 9 software and analysed thematically.

Data were analysed from a symbolic interactionist perspective, in which interviews are understood not as mirror images of an objective reality (the positivist view), but as accounts of experience through which participants in the interview purvey their understandings of the social world under scrutiny (the 'world' of the HIV prevention trial). [25]

Results

Role perception

Informants readily articulated the potential conflicts between acting as a researcher and acting as a doctor, but for those who were medically trained the doctor role was an important aspect of self-perception.

> *In the prevention field we do have a conflict between the social roles, between researchers and participants and doctors and patients…there's a prevailing concept that investigator/participant relationships are essentially a version of the doctor/patient relationship. In the prevention settings, it's not really a good fit – in the prevention setting there are no patients, no one has the disease, and the investigators, even though they may be physicians, they're not really acting exactly like a physician. I1*

[vi] This was question eight in a series of ten broad questions regarding the negotiation of benefits for participants in HIV prevention trials. Informants also made references to the doctor role in answer to other questions regarding participant benefits in trial, which are also included in this analysis.

Identity as a doctor (or clinician or physician) was frequently invoked by informants to emphasis particular lines of moral reasoning or intuition.

> *But me personally I think that everything I was doing made complete sense as a physician as well as a community advocate, as well as an investigator. I1*

Imposed limitations on care

Being a doctor was cited as a rationale for a participant-centred thinking by several participants, for example, when limitations were imposed by funders on non-trial related care that may be provided during a trial:

> *As a medical doctor myself, I think [the limitations are] a bit too strict, but at the same time I can understand the money available for the research is limited.* I2

The perception of having a doctor-like responsibility was not limited to researchers who were medically trained – those whose background was public health also described a strong sense of responsibility toward trial participants and concern at resource-imposed limitations on care.

> *So in terms of the ethical obligations of the trial site, we feel sometimes very, very compromised as to where our role is, is it as a healthcare provider, or is it as a researcher only. And because you grow those relationships with participants, you feel almost obligated to make sure that she gets the treatment and the care that she should be getting. – I10*

Negotiating provision for trial-related injury or illness with the funding body was particularly frustrating for this public health trained PI:

We were certainly conscious of the need to provide for [medical] complications [that arise due to the trial product], but the primary funding agency was the NIH, and the NIH made it quite clear that their funding policies didn't allow for that, and they didn't allow you to purchase insurance, they didn't allow you to pay for healthcare for trial related complications. There were a lot of things that were precluded by their policies, and we found that very problematic. I11

Varying ancillary care standards between sites

Pap smears were a particular point of contention, as cervical cancer is a major cause of death in countries where prevention trials are held, but not all countries provide treatment. A compromise was to conduct cervical screening in sites where there was linkage to treatment, but not otherwise.

We didn't do cervical screening in all of the sites because we couldn't link to treatment in a sustained way .I4

While the rationale for limitations upon care provision were both accepted and deemed acceptable, informants spoke of discomfort:

We made the decision a while ago, after ethical review and consideration and discussion, it was probably inappropriate to offer a [cervical] screening service [i.e. pap smears] if the treatment for that condition couldn't be provided within country…It does make me uncomfortable, but I think it's more reflective of the inequities of healthcare delivery in the developing world, rather than we can't do everything for everyone. –I3

ARV access for seroconverters

The history of the nonoxynol-9 study, which found that the study product increased rather than decreased HIV acquisition, was identified as a catalyst for the development of more extensive benefits packages for participants, including access to antiretroviral drugs (ARV) for those who become HIV positive during a trial. As one informant explained:

> *The nonoxynol-9 experience was still very very fresh in my mind…I felt very strongly we as sponsors have a responsibility to make sure that women who do seroconvert in the trial can get access to really good care… for me it was not a point of discussion even, you* needed *to provide it as sponsors. I2*

International pressure to supply ARV globally made provision within trials less onerous.

> *At the end of the 90s antiretrovirals had a big breakthrough, for the first time treating infection in developing countries… plus the n-9 results became available which increased the risk of infection. I think those two gave a big push to the discussion of what should be the standard of care with regard to HIV. I2*

ARV access for the screened-out

Investigators identified a second group of people who required HIV therapy: those who were screened out of prevention trials for which they had volunteered, on account of being already HIV-infected.

Our main burden of care if you like, our main obligation, the moral and ethical imperative that we felt was more to the women that were coming forward being screened [out], they weren't actually becoming participants of the study, but they were women that had volunteered to join the study, and if they then found that they were HIV positive, we felt …we really have a burden of care to these women, and they're the ones that are far more likely to require antiretrovirals at the point of diagnosis, because they could have been living with the virus unknown for many years. I6

Trial communities fed back to researchers that ensuring people screened-out were referred for care was an important part of building trust.

When we did our first participant event we asked a group of participants to do a play on their experiences in the study, and I was amazed that they spent 20 minutes going on about a woman who had been screened out because she was ineligible because she was HIV positive … and then we took her and put her on antiretrovirals… that showed the level of priority that [study participants] placed on the services that other women who didn't get into the study got. I13

Partnership approaches to providing care

Ancillary care was not always provided directly, but could include referrals through established partnerships.

As I learnt more and more about the needs of participants and the general health profile of the public, I felt that it was my ethical imperative, that I should put something in place to ensure that my responsibility to the trial participant, in full, in the sense that I must ensure that we provide complete healthcare, not

necessarily at the research site, but through partnerships. And I personally believe that that is the ethical thing to do. I10

Building effective partnerships that complemented local service infrastructure consolidated public favourable opinion for the researchers.

The primary healthcare clinics had a large burden of work around family planning services, so we knew that it would be advantageous if we could offer family planning services, so we agreed with them that we would provide study participants with their family planning, and we would complete our own study documentation, but also their district healthcare documentation, so as we are reporting it back through their system as well. So we got all of those services for free, but by our nurses providing it, it supports their service…At the last participant event, the women got up on the stage and they said 'we're disappointed [that the product did not prevent HIV], but we got really good reproductive healthcare, we got pap smears, we got all of these services, these people looked after us and they were good to us'. And that is not necessarily something that people would say about the nurses in the [local] health clinic. I13

Building goodwill through care provision

When care provided within a trial uncovered other readily treatable conditions in a population, this was celebrated.

That's where it is good, when people don't get any care, studies like this can be a win/win to an extent, because you diagnose things that are wrong, and serious, and could be life threatening, had they not come to you. – I5

With the emphasis on delivery of ancillary care, researchers generally described their

focus broadly in terms of having a beneficial impact on individuals and communities, rather than a narrow focus on simply answering a research questions.

> *[Ancillary care is] a good example of how HIV prevention trials can actually impact on the health of the community in a way even go over and above the HIV prevention study, in another disease category.I5*

Discussion

Informants saw provision of medical care as necessary (both ethically and practically) but this created ethical conflict around what people should offer and what they simply could not provide due to constraints of either funding or local infrastructure.

There are several different theories regarding the responsibility of the doctor/researcher to research participants. Chief among these are the fiduciary view,[4] the non-exploitation approach,[5] the partial entrustment model [3] and the capacity-based model.[6]

The fiduciary view posits the health of the participants as the highest priority, [4] and requires that the doctor/researcher uses “reasonable diligence, care and skill” in making judgements that affect the interests of the participant. It does not however specify the parameters of this responsibility in a resource-constrained environment where local care capacity may be below what is recognised as ‘competent medical care’ elsewhere.

In contrast, the non-exploitation approach limits the researchers’ role to the implementing the research protocol,[5] and requires a favourable risk/benefit any provision of ancillary care. This rests on the premise, articulated elsewhere,[26, 27]

that the tension between the therapeutic obligations of the doctor and the scientific obligations of the researcher arise from the adoption of a ‘mistaken therapeutic orientation’ in clinical research.

Informants’ responses in this study were incompatible with this approach. They attest that the tension exists, but do not support the conclusion that the ‘therapeutic orientation’ is mistaken as the health-related benefits were an important aspect of making research acceptable in trial communities.

A vivid case example is provided in the literature by Vallely et al from the MDP 301 microbicide trial.[28] Despite having adopted a standard of care based on locally available best practice within trial sites, a participant with an emergency life-threatening condition unrelated to the study was transported to hospital, admitted and had medicines procured through the private sector for her immediate and on-going inpatient treatment all at the expense of the research site. This exceptional care was provided because the researchers on site felt ”a clear duty of care to the participant and that it was appropriate to use whatever project resources were required to avert a life threatening situation” [p 7], an intuition that echoes Jonsen’s ‘rule of rescue’ – the “moral response to the imminence of death [that] demands we rescue the doomed”[29].

Even so, the best medical interests of individual participants were generally not the key priority for the informants, but one factor to be balanced with several others. The competing factors included the scientific integrity of the trial, limitations imposed by funders, and the constraints of local infrastructure.

The ‘partial entrustment’ model is compatible with the fiduciary view in that it upholds the concept of a duty of care,[3] but it defines the limits of researcher responsibility by analysis of what they call the ‘scope of partial entrustment’. Defining scope, they argue that a trial participant gives permission for the disease under study to be monitored, which involves tests and collection of other confidential material. The responsibility is then mediated (weakened or strengthened) by four factors: participants’ vulnerability, uncompensated risks or burdens, depth (intensity and duration) of the researcher participant relationship, and participants’ dependence on the researchers. [p 1495].

This model can be applied to scenarios described by informants, and is particularly apt regarding the issue of cervical screening (pap smears) in microbicide trials. Cervical screening arguably fits within the scope of entrustment in microbicide trials in that the screening test fits within the range of tests that are done within the trial and it is related to a sexually transmissible infection – HIV prevention trial treat STIs as part of their core function – and HIV prevention trial infrastructure includes laboratory capacity which could readily diagnose abnormal results. With regard to the strength of the claim, microbicide trial participants are typically vulnerable, the risk of the research has been amply demonstrated in the early trials that increased HIV acquisition, and both the duration of the participant-researcher relationship and the level of dependence is generally strong.

The extra factor that needs to be taken into account, however, is the capacity to provide treatment for cervical dysplasia, which goes beyond the normal capacity of a trial site and thus relies on referral to national programs, which did not exist in all

sites. The burden that a particular treatment may place on a research facility was acknowledged in an article further detailing the 'partial entrustment' model by Richardson,[30] adding this as a fifth factor with which to assess the strength of a claim.

Assessing a research site's capacity to respond to such a burden is the focus of the capacity model.[6] The capacity model bases decision making on the urgency of the need, local capacity and internal research capacity. It can be used to better specify both the 'vulnerability' aspect and the 'burden' element in the partial entrustment model, and can provide an approach for dealing with life-threatening episodes such as that described by Vallely et al,[28] thus allowing for the grand (expensive) gesture of life-saving within an otherwise rational model

Returning to the question of treatment for cervical dysplasia, as provision of treatment at trial sites would put a major burden on researchers for a condition not directly related to the trial, the strength of the obligation to provide was weak. The decision to screen only where treatment facilities existed also fits within the framework of screening programs – only screen if there is both a useful test and an available effective treatment.

The emphasis on access to ARV[vii] to trial participants who acquire HIV during a trial (seroconverters) following the nonoxynol-9 trial also fits within the 'partial entrustment' model.[3] The reasoning behind the perceived obligation was two fold:

[vii] 'Access' including referral to treatment programs funded from outside the trial, such as through PEPFAR, the Global Fund, and local governments.

an increased perception of the risk that trial participation entails, and improved access to effective treatment.

Provision of care to those screened-out ranks as a weaker obligation in the 'partial entrustment' model, given the brevity and lack of depth of the relationship. The moral imperative to provide for the screened-out that some participants expressed rests predominantly on a sense of this group's vulnerability – their acute need for treatment, given a presumed longer duration of HIV infection. Arguably this is an example of doctor-like reasoning, placing the interest of a patient – defined as someone needing care – above those of a person who may at some point in the future need care[viii].[31]

Conclusions

The researchers in this study frequently described their ethical deliberations in terms of a doctor-like responsibility. This was not limited to the doctor/researchers in the study – the public health-trained researchers also demonstrated this kind of 'doctorly' reflection. The identification of the 'screened out' is a significant case in point, as the perceived obligation to this group is built on doctor-like moral premise that care is owed to those who most need it, rather than stratifying obligations by the depth of the researcher/participant relationship, which is how it would be framed from a research ethics perspective.

[viii] As Carrese and Sugarman point out, doctors' responsibilities for the sick are emphasised in documents ranging from the Hippocratic Oath to professional codes of ethics.

While participants in HIV prevention trials are not ‘patients’ – they are healthy people at high risk of HIV acquisition – their vulnerability to infection combined with the uncertainties surrounding life-long ARV treatment in resource-poor countries compels attention to their health care needs. Provision of routine primary care in resource-limited settings can ultimately save lives, in addition to the instrumental value of earning the trust that is essential to run such trials.

The nonoxynol-9 experience demonstrated that research participation is inherently risky and that unexpected adverse events can occur with devastating effect. This history pervades ethical deliberation about HIV prevention trials and arguably has predisposed researchers to consider very carefully the benefits that can be weighed against any risks for these populations.

The conduct of HIV prevention trials challenges the notion that a large-scale trial is simply a construct for answering a question. The complexity of how these trials operate within communities, how they sit with regard to national health infrastructure and ultimately how they work with each person who volunteers to participate, impacts on the health status of the communities involved and on the surrounding health infrastructure.

The ‘therapeutic orientation’ in HIV prevention trials appears in this study population to be indivisible from competent research practice. By making concrete and appropriate benefits available to trial participants, the research supports local infrastructure making it acceptable to host communities.

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References

1. Lemmens T, and Miller PB. Avoiding a Jekyll-And-Hyde approach to the ethics of clinical research and practice. *Am J Bioeth* 2002; **2**: 14-17.

2. Miller FB and Brody HB. The clinician-investigator: Unavoidable but manageable tension. *Kennedy Inst Ethic J* 2003; **13**: 329-346.

3. Belsky L, and Richardson HS. Medical researchers' ancillary clinical care responsibilities. *BMJ* 2004; **328**: 1494-1496.

4. Miller PB, and Weijer C. Fiduciary obligation in clinical research. *J Law Med Ethics* 2006; **34**: 424-440.

5. Miller, FG, and Brody H. Clinical Equipoise and the incoherence of research ethics *J Med Philos* 2007; **32**: 151-165.

6. Bright PL, and Nelson RM. A capacity-based approach for addressing ancillary care needs: implications for research in resource limited settings. *J Med Ethics* 2012 (online first).

7. Powers M. 'Theories of justice in the context of research' in Jeffrey P Kahn, ACM., Jeremy Sugarman, ed. *Beyond Consent: Seeking Justice in Research*. 1998, Oxford University Press: Oxford New York. 190.

8. The National Committee to Review Current Procedures from Approval of New Drugs for Cancer and AIDS (Lasagna Commission) *Final Report* (August 15 1990).

9. Baume P. A question of balance: report on the future of drug evaluation in Australia. Canberra: Australian Government Publishing Service, 1991.

10. Abdool Karim SS and Abdool Karim Q. Antiretroviral prophylaxis: a defining moment in HIV control. *Lancet* 2011; **378**: e23-e25.

11. Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; **360**: 971-977.

12. Van Damme L, Govinden R, Mirembe FM, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *N Engl J Med* 2008; **359**: 463 - 472.

13. Feldblum P, Adeiga A, Bakare R, et al. SAVVY vaginal gel (C31G) for prevention of HIV infection: a randomized controlled trial in Nigeria. *PLoS ONE* 2008; **3**:e1474.

14. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science*, 2010. **329**: p. 1168-1174.

15. Padian, NS, van der Straten A, Ramjee G, et al. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. *Lancet*, 2007. **370**(9583): p. 251-261.

16. Padian NS, Buvé A, Balkus J, et al. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. *Lancet,* 2008. **372**: 585-599

17. Auvert, B, Taljaard D, Lagarde E, et al. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLoS Med,* 2005. **2**(11): p. e298.

18. Bailey, RC, Moses S, Parker CB, et al. Male circumcision in HIV prevention - Authors' reply. *Lancet,* 2007. **369**(9573): p. 1598-1599.

19. Gray, RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet,* 2007. **369**: p. 657 - 666.

20. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New Engl J Med 2010;* **363**: p. 2587-2599.

21. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *New Engl J Med*, 2012. **367**(5): p. 423-434.

22. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New Engl J Med*, 2012. **367**(5): p. 399-410.

23. Haire BG. Because we can: clashes of perspective over obligation in the failed PrEP trials, *Developing World Bioeth* 2011;**11**: p. 63-74

24. Cohen MS, ChenYQ, McCauley M, et al. Prevention of HIV-1 Infection with

Early Antiretroviral Therapy. *New Engl J Med*, 2011. **365**(6): p. 493-505.

25. Miller J and Glasner B (2004). The “Inside” and the “Outside”: Finding realities in interviews in D. Silverman (ed) *Qualitative Research: Theory, Method and Practice*. London: Sage, 2004: 125-129.

26. Miller FG, Brody H.. A critique of clinical equipoise: therapeutic misconception in the ethics of clinical trials. *Hastings Cent Rep 2003;* **33**: 19-28

27. Joffe S,Miller FG. Equipoise: asking the right questions for clinical trial design. *Nat Rev Clin Oncol* 2012; **9**: 230-235.

28. Vallely A., Shagi C, et al. Microbicides Development Programme: Engaging the community in the standard of care debate in a vaginal microbicide trial in Mwanza, Tanzania. *BMC Med Ethics* 2009;**10**: 1-17

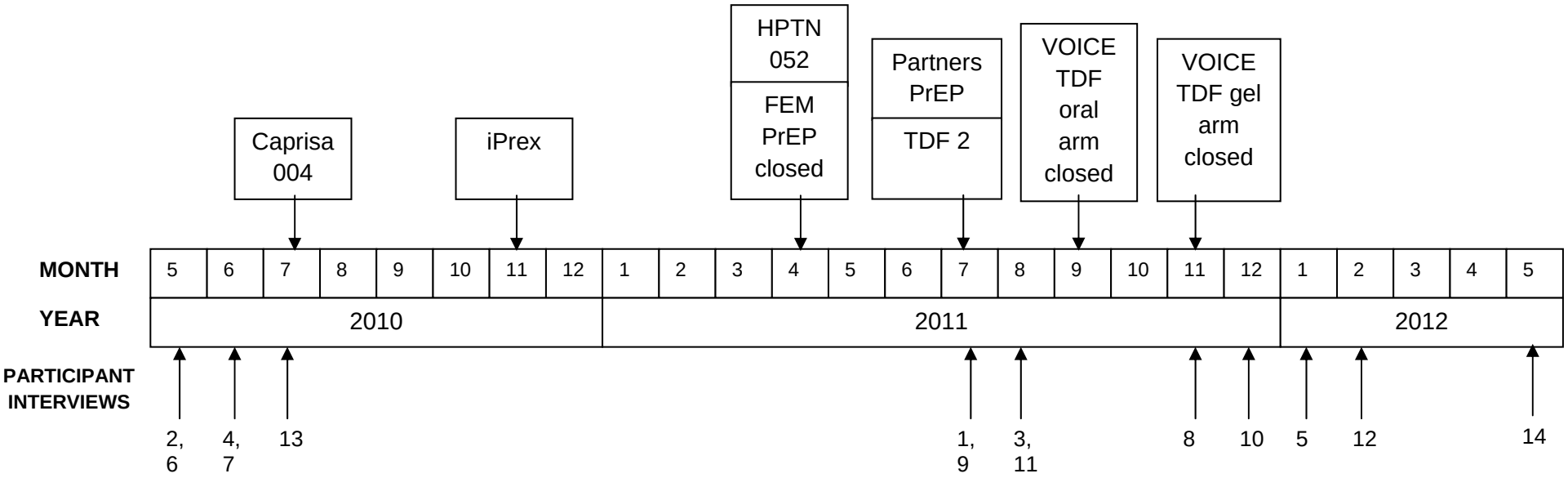
29. Jonsen AR. Bentham in a box: Technology and healthcare allocation. *L Med & Healthcare* 1986; **14**:172- 174

30. Richardson HS. Gradations of researchers' obligation to provide ancillary care for HIV/AIDS in developing countries. *Am J Public Health* 2007; **97**: 1956-1961.

31. CarreseJA, Sugarman J.

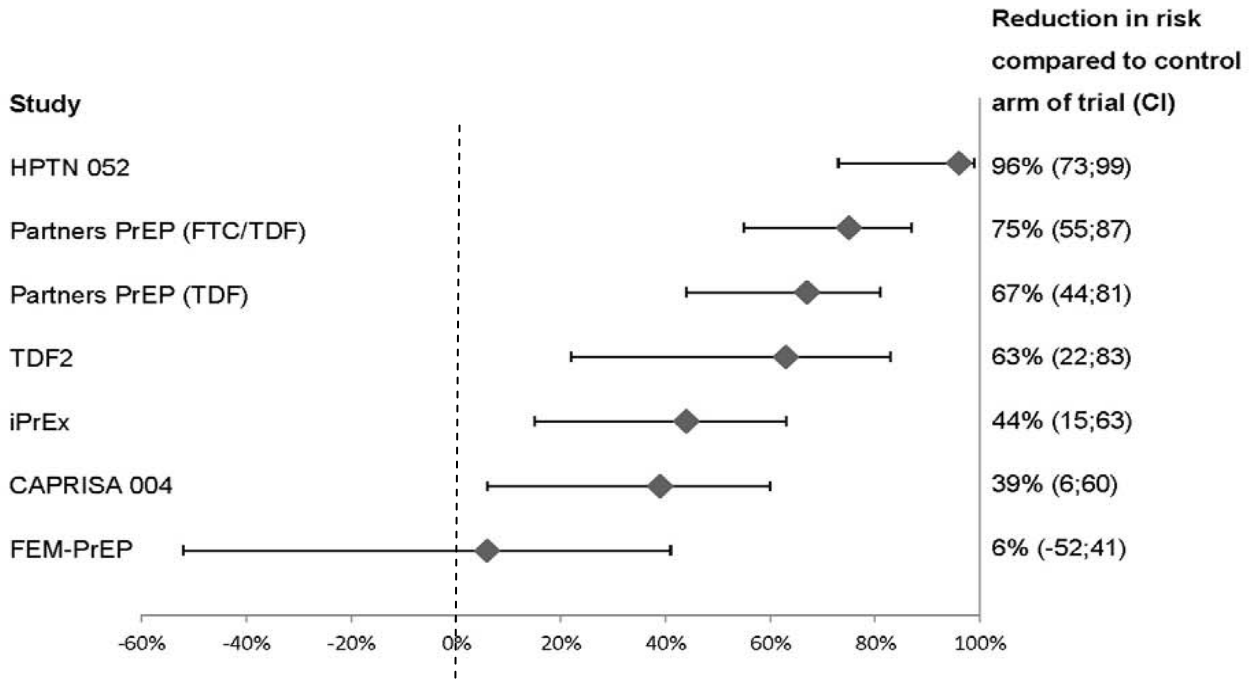
32. The inescapable relevance of bioethics for the practicing clinician. *Chest*. 130(6):1864-72, 2006 Dec., 2006. **130**(6): p. 1864-72.

Figure 2. Timeline showing trial results and interviews



TRIALS:

CAPRISA 004:	Tenofovir gel against placebo. Results: Positive. Efficacy: 39% (95% confidence interval [CI]: 6-60%, p=0.017)
iPrEX:	TDF/FTC combined oral PrEP against placebo. Results: Positive. Efficacy: 44% (95% CI: 15-63% p = 0.005).
HPTN 052:	Early treatment with ARV to prevent transmission to sexual partner against delayed treatment. Results: Positive Effectiveness: 96% (95% CI: 73-99%, p<0.001).
FEM- PrEP:	TDF PrEP against placebo. Results: Negative. Efficacy: 6% (95% CI: -52-41%, p=0.81)
Partners PrEP:	TDF/FTC combined oral against placebo; oral tenofovir against placebo. Results: Positive. Efficacy: 75% with TDF–FTC (95% CI: 55-87%, p<0.001); 67% with tenofovir (95% CI: 44-81%, p<0.001)
TDF 2:	TDF/FTC against placebo. Results: Positive. Efficacy 63% (95% CI 220-83%, p=0.03).
VOICE:	Oral TDF/FTC, Oral tenofovir and tenofovir gel against matched placebos. Results: Incomplete. Oral tenofovir and tenofovir gels arms stopped due to futility.


Study
Reduction in risk compared to control arm of trial (CI)
HPTN 052
96% (73;99)
Partners PrEP (FTC/TDF)
75% (55;87)
Partners PrEP (TDF)
67% (44;81)
TDF2
63% (22;83)
iPrEx
44% (15;63)
CAPRISA 004
39% (6;60)
FEM-PrEP
6% (-52;41)
-60%
-40%
-20%
0%
20%
40%
60%
80%
100%

Part 2, Chapter 3

Standard of prevention in the real world: A qualitative study of principal investigators in HIV biomedical prevention trials

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Abstract

Background

UNAIDS Guidelines require that participants in HIV prevention trials are provided with 'state of the art' risk reduction measures. Published data showing that new HIV prevention strategies are highly, but not completely, effective problematize 'standard of prevention' packages that provide access to condoms and counselling only. This qualitative study asks how principal investigators on HIV prevention studies determine appropriate standards of prevention. It builds on previous work mapping standards of care in HIV prevention trials by investigating how decisions were arrived at, in addition to reporting what was decided.

Methods

Semi-structured interviews were conducted with fourteen principal investigators of biomedical HIV prevention trials. Interviews were transcribed, coded, and analysed thematically using pre-determined categories derived from the ethics literature and spontaneous coding.

Results

A spectrum of views was given by informants as to how standard of prevention should be determined, ranging from an ethical requirement to include newly validated technologies as soon as feasible to a perceived need to reduce the prevention package to make it more like real life, thus enhancing conditions for subsequent trials. Each informant argued her position with reference to the feasibility of ongoing studies, the need for conclusive data on the effectiveness of preventive interventions, perceived

duties to trial participants and regulatory requirements. Some saw re-consent as the critical issue in ongoing trials when relevant data from other studies was released.

Conclusions

There was no ethical consensus about the standard of prevention among principal investigators. Rational arguments were made to support disparate positions. This suggests a need to examine and articulate the ways that the narrow aims and obligations of a research study sit within the broader context of disease burden and inequitable access to health care in the resource-poor world, to address how research should proceed to ensure justice and feasibility.

Introduction

Whether participants in HIV prevention studies should receive the best possible standard of care or a 'good enough' package is a normative issue in bioethics that is so contentious that even the key guidance documents take different positions. Best possible, or 'state-of-the-art' packages are called for in the UNAIDS 2007 guidelines, while the HPTN guidelines stipulate that a basic prevention package is acceptable – if it is effective, achievable and accessible (Rennie, Sugarman et al. 2009).

'Standard of care' is a broad term that encompasses the HIV prevention package offered to all trial participants (now called 'standard of prevention'), care for non-trial related conditions (ancillary care) and access to antiretroviral therapy for those who acquire HIV during a trial.

'Standard of prevention' is particularly important now in the light of a growing body of evidence on the efficacy of HIV biomedical prevention. Antiretroviral drugs have shown efficacy as preventive agents in five studies using treatment-as prevention or pre-exposure prophylaxis strategies[1] (Abdool Karim et al. 2012, Grant et al. 2010, Cohen et al. 2011, Baeten et al. 2012, Thigpen et al. 2012), while circumcision[2] has shown efficacy in three studies (Auvert et al. 2005, Bailey et al. 2007, Gray et al. 2007). Both circumcision[3] and treatment-as-prevention have been recommended by UNAIDS/WHO for HIV prevention (UNAIDS WHO 2007; UNAIDS WHO 2012). Oral pre-exposure prophylaxis (tenofovir/emtricitabine as a

[1] 'Pre-exposure prophylaxis' includes both topical (tenofovir gel as a vaginal microbicide) and systemic use (tenofovir/emtricitabine in combined oral form).

[2] We adopt the term 'circumcision' rather than 'medical male circumcision' because the latter suggests that there is a corresponding 'female' form of circumcision.

[3] The caveat regarding circumcision in HIV prevention is that it is only recommended in generalised, high burden epidemics.

combined tablet) – henceforth referred to as 'PrEP' – was approved for prevention of HIV in women and men at risk of HIV in the United States on July 16, 2012. The US Food and Drug Administration's approval of PrEP and the UNAIDS/WHO recommendation regarding circumcision and treatment-as-prevention raise the issue of whether any or all of these interventions should be included 'standard of prevention' in HIV trials (Food and Drug Administration 2012).

This article reports findings from a qualitative study concerning the negotiation of benefits for participants in HIV prevention trials. The study is based on interviews with principal investigators of prevention trials held between 2000 and 2011, the period in which a wide range of HIV prevention efficacy trials testing a range of strategies were conducted. The FDA approval of PrEP had not occurred at the time that the interviews were conducted, but the issues associated were discussed hypothetically.

The study documents how principal investigators' recollect and represent their practice with respect to negotiating participant benefits within the ethically and logistically fraught context of managing research programs that recruit people vulnerable to HIV acquisition in resource-limited settings. Critical analysis of this data raises important normative questions such as problems with evidentiary standards, equipoise and the structural and inter-sectoral factors that affect access to medicines (whether approved or not approved) in situations of scarcity, poor healthcare access and HIV stigma.

Background

Controversy over standards of care erupted in 1997 over mother-to-child prevention trials in the developing world that tested experimental regimens against placebo controls (Lurie and Wolf 1997; Angell 1997). The use of a placebo control was

controversial because several years earlier the seminal PACTG076 study had shown an intervention to be effective (Connor et al. 1994). Critics of the placebo-based trials argued that they constituted a double standard in research between rich and poor countries. Defenders of the trials argued that the PACTG076 regimen was not feasible in the developing world and that the critical research question was whether the experimental regimens were better than nothing (e.g. Varmus and Satcher 1997).

In the late 1990s, the new-found efficacy of combination ARV therapy in treating HIV disease catalysed a surge of research interest in biomedical prevention. The issues raised by the mother-to-child prevention trial led to heightened ethical scrutiny of other HIV prevention trial design. Two key questions were raised. One was whether researchers had an obligation to decrease the likelihood of HIV acquisition in prevention trials by facilitating access to condoms, safe sex counselling and treatment for sexually transmissible infections (STIs). The other question was whether those who acquired HIV during a trial should be provided with access to life saving ARV therapy. Provision of ARV was the more contentious question, particularly because it had massive resource implications at a time when donor programs had not been established and national health systems were not supplying ARV (Slack et al. 2005).

The UNAIDS ethical guidelines of 2000 (reprinted 2004) stipulated that condoms, counselling and STI treatment should be made available to trial participants. Access to ARV was seen as subject to negotiations that turn on three key factors: the level of care available in the sponsoring country, the highest level of treatment and care available in the host country, and sustainability of treatment (UNAIDS 2000).

Notably, neither the VAXGen phase III vaccine study published in 2005 nor the COL 1492 phase III microbicide study that ended in 2000 facilitated access to ARVs (rgp120 Vaccine Study Group 2005; Van Damme et al. 2002)[4]. Indeed, COL 1492 investigators sought guidance from an ethicist on this question, and were told that to do so would constitute 'undue inducement' as it was a benefit that trial participants could not access except through the trial (Van Damme 2010)

Community opinion, however, was that antiretroviral access should be provided. By the early-to mid 2000s three separate trials of a new HIV prevention strategy, pre-exposure prophylaxis or 'PrEP'[5], were stopped due to community protest. While the reasons for the trial closures were complex and multi-factorial, the issue of access to antiretrovirals was cited as a key concern in each[6] (Page-Shafer et al. 2005, Forbes and Mudaliar 2009, McGrory, Irvin and Heise 2009, Haire 2011).

Increased global availability of antiretroviral (ARV) therapy through the WHO initiative aimed at treating three million people by 2005 (WHO 2012), and donor programs including the Global Fund and PEPFAR, allowed a consensus position to emerge regarding standard of care. Participants in prevention trials were provided with access to condoms and safe sex counselling, and people who acquired HIV during the trial (seroconverters) were linked with care programs as needed for ARV access (Macklin 2006, Heise et al. 2008). The provision of these services varied:

[4] The study product in the COL 1492 study, nonoxynol-9, was subsequently found to increase risk of HIV acquisition.

[5] Pre-exposure prophylaxis is a strategy that uses antiretroviral drugs in HIV negative people to prevent infection. The ARVs tested as PrEP are tenofovir alone, and tenofovir with emtricitabine combined in a single tablet.

[6] This concern was a perception rather than a reality in the case of the Cambodia trial, where access to ARV for seroconverters was secured for a limited time post-trial.

some trials consolidated links to care more thoroughly and proactively than others, and quantity and quality of prevention services also varied (Heise et al. 2008). Nevertheless, there was broad acceptance that these services *should* be provided, even though concerns were occasionally expressed about their possible negative impact on results such as prevention services reducing HIV incidence in the trial population to a degree hard to predict and thus factor into sample size calculation (e.g. Padian et al. 2008).

Accordingly, the debate about the standard of prevention (the package of preventive interventions offered) slumbered while there was a lack of evidence supporting new HIV prevention methods. It has been reignited, however, by the recent publication of evidence that a range of new prevention measures are partially effective. These include tenofovir gel (Abdool Karim et al. 2010), pre-exposure prophylaxis (Grant et al. 2010, Baeten 2012), 'treatment-as-prevention' (Cohen et al. 2011) and circumcision (Auvert et al. 2007, Bailey et al. 2007, Gray et al. 2007).

This study explores the negotiation of the standards of care for research participants from the perspective of principal investigators of HIV biomedical prevention trials. Drawing on a series of interviews with principal investigators, it documents the structural factors they identified as affecting the benefits that are available to participants, and their views on how partially effective biomedical technologies may introduce a tension between research ethics and the ongoing feasibility of HIV prevention research. This article focuses on standard of prevention rather than the other aspects of standard of care.

Methods

Twenty-eight efficacy trials of biomedical HIV prevention (either phase III or IIb) were identified between 2000 and 2011 through the Current Controlled Trials and

clinical trials.gov databases. The search term ‘HIV prevention’ was used, and efficacy trials (phases III or IIb) were selected from the results. Principal investigators and first authors of key publications were considered eligible for the study and were contacted by email and invited to participate in a semi-structured interview. The sample is purposive, as some eligible individuals did not respond to repeated invitations to participate, and some declined.

All of the interviews were conducted by the first author. Nine interviews were conducted by telephone and five were conducted face-to-face. In the interview, informants were asked to describe how they negotiated benefits for research participants in particular trials. They were also invited to speak to the following specific issues:

- How they formed their views about obligations to participants
- The role of guidelines and ethics literature in informing their views
- Structural factors that affected the provision of standards of care
- How the accumulation of efficacy data affected standard of prevention in ongoing and future trials
- Whether they were satisfied with how negotiations had been conducted
- Whether they felt that planned standards of care were achieved.

Interviews were conducted between May 2010 and May 2012. During this period, positive efficacy data from five trials was published (see figure 1, timeline). This was punctuated by surprise futility findings from two other trials (FemPrEP and

two of the three active arms of VOICE). The interview schedule was adapted to capture key issues raised by these new developments in the field.

Interviews were audio taped, transcribed, checked for accuracy, and coded with N-Vivo-9 software, using a combination of inductive and pre-determined codes, which were then analysed thematically. Predetermined codes were derived from the ethics literature on standard of care/prevention, and included equipoise, evidentiary standards and participatory practice. Inductive coding was a sentence by sentence process that categorised concepts as they were framed by the participants, such as 'real world', 'attention to form not substance' and 'too-good care as inequitable'. All coding was done by the first author.

Data were analysed from a symbolic interactionist perspective, which treats interview data as accounts of experience through which the interviewees communicate their understandings of the social world (the world of the HIV prevention trial), as distinct from a positivist perspective, which would view interview data as a mirror image of an objective reality. This perspective recognises that interview is a particular interaction that inflects the responses given, while nevertheless allowing that the participants are discussing a reality that exists outside the interview (Miller and Glasner 2004).

Quotes from interviews have been anonymised, and all informants are referred to as 'she'. The study was reviewed and approved by the ethics committee of the [name of institution]

Results

This analysis is based on interviews of 14 male and female principal investigators who between them had worked on more than 20 HIV prevention trials. Of the principal investigators interviewed, two were 'in-country' investigators, meaning that

they headed the study at a particular trial site, but did not have oversight of the trial as a whole. The remaining 12 informants oversaw whole trials and in some cases networks of HIV prevention trials. Most of these interviewees had been a principal investigator or a senior member of the research team on more than one study

Informants had a spectrum of opinion about how best to approach standard of prevention in future trials. They expressed a range of different views about the role of research in the HIV prevention endeavour, and about optimal processes for achieving common goals, such as access to ancillary care and/or antiretrovirals.

At one end of the spectrum was the view that the prevention package offered in clinical trials actually distorts clinical trials for new prevention modalities by reducing HIV incidence in the trial population to an extent that would not occur outside the trial context:

> *We need to concentrate on the thing we want to measure and peel back from offering everything. – P1*

The practice of optimising HIV prevention[7] for participants was criticised by some respondents on the grounds that it creates a set of conditions that differ from those in the 'real world' outside the trial for which new HIV prevention technologies are intended:

[7] Comprehensive HIV prevention comprises condoms (ideally male and female versions), STI treatment, and behavioural strategies such as partner reduction, 'negotiated safety' (agreements about condom use outside of a primary relationship), withdrawal before ejaculation and 'strategic positioning', where an HIV negative man opts to penetrate rather than be penetrated by a male partner of positive or unknown serostatus.

What we have created is a massive gap between the real world and clinical trials. – I1

This view is elaborated further by a second informant:

The more you provide to the control arm, the more difficult it becomes scientifically then, to come up with a reliable result in terms of the impact of the intervention itself…And that means that ironically, the better you are at doing that, the more you're undermining the value of the trial itself, because you may then be unable to show that the intervention is effective, and that might then deny the intervention to very large numbers of people and communities in the future. I –I2

In other words, comprehensive standard of prevention packages make it difficult to demonstrate efficacy of a preventive measure.

A third position articulated by Informant 14 is that so long as placebo controls best meet the requirements of regulatory bodies, their use is ethically justified by the public health need for a new effective and acceptable HIV prevention method:

[T]he FDA has standards no matter where the trial's conducted, about physical standards in controlled trials. And that's how you test two medicines. So first you have to see if it works at all, you have to test against the placebo, and then you want to test it to see if it's better than something else before [licensure]… I can't envision a time when there's never going to be a need for any placebo controlled trial. –I 14

At the other end of the spectrum was the view that in order to be sure that an experimental intervention made a real difference, it needed to be compared to best

practice prevention. Thus, an optimised prevention package can be viewed as a sound epistemological decision as well as an ethical one:

> *We wanted to be able to show that our intervention for HIV prevention added to the benefit of existing care… above and beyond everything else that we know how to do. – I3*

Informant 3's position contrasts with that of Informants1 and 2, who argue that experimental interventions should be compared to prevention packages that are closer to standard practice in the host country, rather than 'best practice', for implementation purposes.

The rationale for the argument provided by Informant 1 is that prevention services within trials should approximate locally available prevention. Informant 11 introduces the notion that any improvements to local practice should be sustainable in the community when the trial concludes:

> *I think you have to be careful about getting ahead of the curve, because if you do start providing services that cannot be sustained after participants exit the study, you create another ethical dilemma.* –I11

As Informant 4 states,

> *It's a very fine balance between the elevation of the standards just for the duration of the study, versus elevation and advocacy for standards that are higher than when you got there. So, to me, whatever you do, you have to leave your participants in communities better off. – I4*

This notion of sustainability introduces the idea that a prevention trial can operate to some extent at least as a capacity- building development project, rather than simply as an experiment.

Informant 3 argues explicitly for the trial as an exemplar of best practice prevention:

> *We're better off being advocates for providing the best possible prevention care, and at the very least improving it in every environment. If something is not practical, or not feasible for a given population, then no I don't think you have to provide something that is not feasible. But I think that most things that we are talking about are feasible…it's just a matter of lowering the price and raising the funds to make these things available.– I3*

Informant 9 argued that high standards of evidence were needed to ensure that scientific questions were answered decisively, and that accepting preliminary or non-definitive evidence as disturbing equipoise jeopardised the production of knowledge:

> *In every trial, the herd is going to make the decision [to change standards] during the course of the trial, where the very question is being addressed. This is the danger and the tension of equipoise. I 9*

The tension between the scientific imperative to answer a research question and the ethical imperative to maximise benefits for their participants was articulated by another informant as balancing between shades of grey.

> *I think it's a fine line between the importance and the impetus and the imperative for your research question, versus all the other things that we can potentially help to improve [conditions for participants and their*

communities], how much of that is directly related [to the trial], how much of that is indirectly related, how much of that is essential, how much of that is aspirational. And I think that's where things get varied between lighter and darker shades of grey, for some people, and for some people it becomes black and white issues. I4

Informants frequently referred to ambiguity and ethical 'grey areas', particularly those interviewed after the FemPrEP trial. FemPrEP, which tested pre-exposure prophylaxis (the combination of tenofovir and emtricitabine) in African women, was stopped due to futility in April 2011 (Celum and Baeten 2012), despite evidence from three randomised controlled trials in different populations showing efficacy (Grant et al. 2010, Roehr 2011).

After the Fem-PrEP result, rather than talking about *whether* 'state-of-the-art' interventions should be offered as standard of prevention, the participants focussed on *how* 'state-of-the-art' might be determined for new prevention interventions.

It's a genuinely difficult issue, as to what stage placebo controlled trials become inappropriate or unethical or both …. And indeed even when we do have sufficient evidence, is it only when the product is licensed and available that a placebo controlled trial would become unethical, or is the mere fact that the evidence is there, sufficient to make further trials inappropriate? I5

There are two aspects to the problem posed by Informant 5's question: the strength of the evidence and the difficulty of pinpointing exactly when equipoise evaporates.

One investigator summed up the new tension from conflicting sources of authority thus:

> *Your ethics committee says you can't have a placebo controlled study, and your regulator says that's the only study we will licence the products on. So what do you do? I8*

In the field of HIV prevention trials, research ethics faces a tricky epistemological question: Can equipoise persist in light of positive efficacy results from a well-conducted randomised controlled trial?

Researchers enrolling heterosexual men in their prevention trials were the first to grapple how the loss of equipoise should affect clinical trial design, as medical male circumcision was the first intervention that warranted consideration for inclusion as part of a prevention package in other trials. The issue remained contentious, however, even after evidence from three randomised controlled became available:

> *We introduced circumcision before WHO and we were criticised because we went before anyone, because we thought the nature of the data was overwhelming. I8*

In Informant 11's trial, circumcision was provided through referrals and in line with national guidelines rather than proactively, which meant that it was not uniformly available at all trial sites at the same time:

> *With male circumcision, it took Uganda longer than Kenya for example, to adopt the national policy. Until they really did adopt the policy … we were limited in our ability to actually make it available. I11*

Informant 10's study offered medical circumcision to male participants using an objective evidentiary standard, while Informant 11's study used referral to national infrastructure. This meant relying on a local standard, and participants' access to the procedure was therefore determined by where they lived.

The circumcision example illustrates the kinds of inequities that can result from depending on local infrastructure to define and implement a standard, but the issues confronting the field now with PrEP are different. Firstly, only the US has approved PrEP; and secondly – despite successful trials conducted in low- and middle-income countries (Kenya, Uganda, Botswana, Brazil, Ecuador, Peru, South Africa and Thailand) the question arises as to whether PrEP would, could, or should be provided as a standard in resource-poor countries.

As Informant 5 says,

> *I think where we get into ambiguity is … let's say a new intervention has shown some level of effectiveness, but clearly isn't imminently available in the communities where we're doing our studies, and may never be – to what extent should that then become part of your prevention package? I5*

Both Informant 5 and Informant 10 articulated the need to rationalise concepts of 'efficacy' as demonstrated in statistical terms, with an assessment of whether or not a result is clinically important. For Informant 10, this meant the magnitude of the effect of the intervention (efficacy of at least 50%), while for Informant 5, it was a balance between improvement the new product offered over existing prevention combined with a real ability to make the product available in the community for which it is intended.

Cost-effectiveness was also an issue. As Informant 8 states:

It would be horrible if we asked the government to register Tenofovir gel at seven rand or one dollar a pop, and then you find out later that it was only 6% effective [the lower end of the CAPRISA 004 confidence interval].

Discussion

The key issues relating to standards of prevention identified by the informants in this study were the perceived conflict between ensuring sustainability of interventions and improving local standards, the generalisability of findings, equipoise and the necessity to obtain a clear scientific result . The shifting evidentiary landscape, with new trial data being released during the time period, and the normative ambiguities created by the differences between ethical guidelines and the flexibility within the guidelines regarding when or if new standards must be adopted, created a context in which there was no undisputed approach as to how new trials should be designed (Philpott et al. 2011).

Real worlds: sustainability, or improvement of standards?

The concept of the 'real world' was frequently invoked by participants. Sometimes it was used to make a point about an unbridgeable gulf between standards of health care in resource-rich and resource-poor settings/countries. Sometimes it was used to make the point that one 'reality' is codified in the written health care standards of host countries, while a different 'reality' is observed in clinics where these written standards are not always met. Thus if a study opted to ensure implementation of the codified healthcare standards – such as hepatitis B vaccinations, or regular pap smears – they were in some cases "rachetting up" the actual care delivered in the community (Benatar and Singer 2000).

The gulf between actual health care delivery in a community and the formal standard documented for that country could also play out in a different way. In one study, the formal standard for access to ARV changed (i.e. the revised standard stipulated that ARV should be provided at a higher CD4 count than before). The principal investigator responding by 're-consenting' the participants – that is, she informed them of the revised standard, reminded them that they were free to leave the study in order to benefit from it, and formally obtained their renewed consent to remain in the trial in the light of the new information. The 'new standard' was not in any practical sense available, however, as the countries in question did not have a new influx of drugs to respond to increased demand (though the trial site did offer to assist with identifying access points, and four participants took up this offer). In this case, the notional autonomy of the participants to remain in the study or to leave to pursue a (largely unattainable) standard was invoked, but unsurprisingly, participants overwhelmingly opted to stay in the study (Cohen, McCauley and Sugarman 2012).

Generalisability: the adherence issue

Randomised controlled trials (RCT) are designed to produce results that are generalisable to comparable populations (Little 2003, 7). Phase III trials (and to a lesser degree, IIb trials), aim to establish the efficacy of an intervention. Evidence of 'efficacy' means evidence that the intervention being evaluated produces a desired outcome under optimal conditions where confounding variables are controlled for by the experimental design (Compher 2010). Recent evidence about the lack of adherence to preventive measures in HIV trials – including successful ones such as iPrEx that that produced evidence of efficacy results despite, rather than because of,

adherence issues – suggest that, despite intensive efforts, the trial context may not facilitate adherence. Participants are constantly reminded that it is not known whether the intervention works, and that they might be receiving a placebo rather than the experimental intervention. As Kippax and Stephens point out (2011, 394), biomedical prevention that relies on sustained use has major behavioural and structural components because effectiveness depends on access to, acceptance of and adoption of the intervention.

PrEP showed efficacy in heterosexual women in the Partners PrEP and TNF 2 studies but not in FemPrEP and VOICE[8], and tenofovir gel showed efficacy in CAPRISA 004 but not in VOICE. (VOICE used the same product as CAPRISA 004 but a different dosing schedule). Arguably these disparate trial results reflect different acceptance and uptake of the study product in their respective populations, and different perceptions of risk affecting the motivation of participants to take a pill or use a gel. Adherence to the study product is critical for trials, but there is accumulating evidence that trial participants do not accurately report adherence or lack thereof (Van Damme et al. 2012, Grant et al. 2010). Arguably then these trial results reflect the products' *effectiveness* in particular populations rather than providing a measure of *efficacy* that can be generalised (Donnell 2012).

When trials produce different findings as to the efficacy of a preventive measure, they augment rather than reduce uncertainty. These vastly different trial results for the same interventions, if understood as 'efficacy' results, add up to a state

[8] Tenofovir PrEP was efficacious in TNF 2 but not in VOICE, and while tenofovir/emtricitabine PrEP was futile in FemPrEP, it was efficacious in TNF2 and Partners PrEP. The efficacy tenofovir/emtricitabine PrEP in VOICE is not yet known.

of uncertainty about the efficaciousness of the interventions. If understood as 'effectiveness' studies, however, the picture is somewhat different: that the efficacy of the intervention is impacted negatively by the particular context of the less successful trials – as the FDA has recently noted in its review of tenofovir/emtricitabine for HIV prevention:

> In sum, individuals may have any number of reasons or influences that increase or decrease adherence to medications. Some believe that PrEP clinical trials represent ideal circumstances that cannot be replicated in a real world setting. At this time, however, it is not known if PrEP adherence is better or worse outside the clinical trial setting (The Review Team for NDA 21-752/S-30 2012).

Equipoise

Equipoise has traditionally been defined as a state of uncertainty that arises when there is no reason or evidence to prefer one intervention to another (e.g. Fried 1974, Freedman 1987). It is a contested concept. Some see it as the premise that justifies clinical research: the clinician/researcher can randomise patients because there is genuine uncertainty as to what is the best course of action. On the other hand, some bioethicists see it as unnecessary to ethical research as the public good of health research requires no justification (Miller and Joffe 2011). But assuming that we accept equipoise as a valid concern in research (and none of the PIs in this research questioned this), the big questions about equipoise are who is meant to have it, and how do you know when it is gone?

Equipoise is increasingly understood less as an individual disposition than as a consensus view held by a community of experts (or 'the herd', Informant 9 describes it). This notion of equipoise is somewhat vague in that the community is not clearly

defined, and nor is the process by which consensus is achieved. One response to this problem in discussions about standards of prevention is to "hitch" equipoise to a standardised measure, such as a regulatory standard, or ethical guidelines.

Guidance point 13 of the UNAIDS/WHO Ethical Considerations in HIV Biomedical Prevention trials (2007) states that there is an obligation to provide "access to all state of the art HIV risk reduction methods … to participants throughout the duration of the biomedical HIV prevention trial" and goes on the state that, "new HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities". There are several points of flexibility here: firstly the addition of new risk-reduction methods is subject to consultation, and second, there are two separate conditions that are to be taken into consideration: scientific validation, or approval by relevant authorities. Does scientific validation mean data from one trial, or two, or more? Does 'relevant authorities' mean approval by any regulatory or normative boy, or does it mean approval by the national regulatory authority of the country or countries in which the trial takes place – and what if several countries are involved, and some regulatory bodies have approved and intervention while others haven't?

These questions are particularly pertinent now that the FDA has approved TDF/FTC as PrEP, while other regulatory bodies have not. While it stretches credulity to argue that equipoise persists once an intervention has been approved by a body such as the FDA, the framing of Guidance point 13 arguably provides a source of moral authority for delaying the introduction of

a ‘state-of-the-art’ intervention until such time as it is listed in national guidelines.

Generalisability: should prevention standards be optimised?

The extent to which findings can be generalised to the ‘real world’ outside the trial is one of the classic epistemological problems with experimentation (Ashcroft 2004). Informants in this study had different perspectives as to whether standards of prevention should be optimised or kept closer to pre-existing local standards. Recent efficacy trials of HIV prevention have reduced HIV incidence in trial populations, regardless of whether the experimental intervention is effective, due to the increased emphasis on providing and promoting existing prevention methods such as condoms and STI treatment (e.g. Peterson et al. 2007, Feldblum et al. 2008). An epistemological problem particular to HIV prevention trials is that it is not possible to discern (a) which sex acts actually involved risk of HIV acquisition for a participant (i.e. when s/he had sex with a person with an HIV viral load high enough to cause infection); or (b) whether the experimental intervention/placebo was used, or a condom, or both experimental intervention/placebo plus condom, during the actual risk event/s. This raises complex issues for the interpretation of trial results particularly as participant self-report regarding use of prevention interventions may be unreliable (Van Damme et al. 2012, Grant et al. 2010), and HIV exposure does not necessarily cause infection (Boily 2009).

Randomisation, together with sufficient sample sizes, are the tools that are intended to isolate the efficacy of an experimental intervention regardless of the standard of prevention available to participants in intervention and control arms. If

however standards of prevention are adopted differently in control and intervention arms, this might confound trial findings. Further, if the intervention itself is of very marginal benefit, this might be masked by enthusiastic uptake of a standard of prevention in a trial community. Weeding out marginally effective products is a problem if a biomedical intervention is deemed inherently better (i.e. cheaper and more sustainable) that a barrier-and-behavioural intervention.

The argument against optimised prevention as made by Informants 1 and 2 echoes that made in a *Lancet* review article by Padian and colleagues (2008, 593).

> To comply with ethical guidelines, we have reduced our ability to assess new prevention methods by comparing them to the best available prevention standards of care (e.g., limitless sexually transmitted infection treatment; frequent, individualised, and expensive condom counselling). Such strategies are not representative of the standard of typical prevention services in the community and are not sustainable after completion of the trial. The complexity of the design is increased by addition of these packages to the intervention, so at best we can measure the marginal benefit of the new intervention compared with the effect of the ideal prevention package. Thus, the ability to detect any effect of interventions postulated to be moderately effective (e.g., <50%) is reduced. (Padian, Buvé, Balkus et al. 2008, 593)

First author of the article quoted above was the principal investigator of the MIRA trial which tested the diaphragm as an HIV prevention method and found that it was no more effective than placebo (Padian et al. 2007). Sub-analysis showed that women in the control arm of the trial used condoms more consistently than those in the intervention arm of the trial. There has been speculation that greater condom use

in the control arm combined with lower than expected adherence to the study product in the active arm, may have produced a flat trial result even if the diaphragm had modest efficacy. This shows that the randomisation process may not smooth out differences between experimental and control groups, particularly when a study is not blinded, as was the case with MIRA.

Arguing along similar lines to Padian, Informants1 and 2 privilege a research outcome – optimising the chances of getting a positive efficacy result in a trial – over the researchers' putative obligation to minimise HIV acquisition in order to hasten access to a (presumed) partially effective product.

Taking the opposite view, Informant 3 argues for optimisation of the standard of prevention on the basis that an optimised standard could show that the experimental intervention had an effect over and above '*everything else that we know how to do'*. In other words, if a standard of prevention does not include an element known to reduce HIV acquisition – say STI treatment, or post-exposure prophylaxis – and was shown to be effective against that prevention background, it would remain unknown whether adding in the missing element/s would be as good as, or better than, the experimental intervention.

Informant 3, in advocating the 'best possible prevention care' within a trial privileges the improvement of local standards by adopting best practice for the trial duration at least, again in contrast to informants 1 and 2 who privilege getting a research outcome. Both positions are ethically defensible, but each defines its key responsibility slightly differently. In one case, production of knowledge takes precedence; in the other, maximisation of benefits to participants takes precedence.

In theory, if a trial relied on prevention programs that were already operating in the host community rather than optimised programs, it would be more likely to detect the efficacy of a marginally effective product. Efficacy studies of HIV prevention take place in communities that have a high HIV incidence, so it is highly likely that background HIV prevention programs in these communities are ineffective, particularly for the population(s) identified as being at high enough risk to participate in a prevention trial. A biomedical product that is proven efficacious against a background of suboptimal behavioural prevention programming could eventually have a population health benefit in that *particular* population if the intervention was low-tech, readily available, user-friendly and affordable. But as well as failing to optimally protect research participants, such an approach would create a new problem for generalisability of findings. There is no *single* 'real world' HIV epidemic. Epidemics have social, cultural and political dimensions (Kippax and Stephenson 2012), and the relative successes of prevention programs depend on these factors as well as on the underlying incidence of infection. Therefore, *not* optimising the prevention package (whatever that entails in a particular community) arguably makes it harder to extrapolate a result outside the trial community.

'Getting ahead of the curve' is an ethical dilemma that Informant 11 identifies, arguing that setting up enhanced prevention services for which there is no assured funding post-trial potentially leaves a community worse off at the trial's conclusion due to withdrawal of some services. From a utilitarian perspective what ethically important here however is that the community is *not* worse off than it would have been *had the trial not taken place*. Whether the trial has brought benefits and services which can be sustained after its completion is a different issue. If a trial enhances HIV prevention services for its duration, the outcome is reduced HIV acquisition.

Reduced HIV acquisition for the time period of a clinical trial is a real benefit that affects not only those who did not acquire HIV during the trial, but their sexual partners who may have been at risk post-trial. Thus it impacts on HIV incidence in an ongoing beneficial way, even if there is a perception of services being withdrawn at the closure of the trial. Reducing HIV incidence is a real and tangible benefit.

The argument to limit available services during a trial so as to ensure sustainability post-trial contrasts with the view that the prevention trial is in itself a catalyst for change that can (and arguably should) improve health care standards.

Notably, most though not all of the informants who framed prevention trials as an opportunity to improve services in host communities lived and worked in countries that hosted HIV prevention trials. 'Insider' status in a host community appeared to be linked to a greater sense of agency with regard to capacity building, possibly because these investigators would themselves be there post-trial to continue to implement services

Conclusion

International ethical guidelines enshrine the principle that research participants are entitled to the best current treatment or prevention standard regardless of where they live (World Medical Association 2008, UNAIDS 2007). Nevertheless, there is ongoing dispute whether this is a binding ethical norm or an aspiration (e.g. Rennie and Sugarman 2009). Operationalising 'state of the art' prevention in the context of HIV biomedical prevention trials is fraught, and requires a series of judgements on controversial issues.

The informants in this study negotiated complex systems that structured what was and was not possible in their particular studies, including funding constraints, regulatory systems, host-country health systems, guidance documents and ethical review processes, in a context where the realm of HIV biomedical prevention was in flux, with new and sometimes apparently conflicting data being released from other studies.

This study shows that there is still division at the level of principle as to whether standards in research should be universal, local or somewhere in-between. More importantly, it shows that 'best current' or 'state of the art' are not clear-cut judgements. The issue of how a 'validated' or 'proven' intervention is defined is critical to how decisions are made regarding standards of prevention, and the current lack of clarity on evidentiary standards means that regulators are the default deciders.

Other factors can also impact on standards of prevention. It matters, for example, whether a research project is based at a comprehensive health facility in the host country. This was evident in trials that have sought to provide male circumcision, and were delayed by the slow introduction of a host country program.

There are different conceptions of what a research study can or should achieve. Does the importance of answering a scientific question justify the ongoing use of placebo controls in circumstances where access to new technologies is not meaningfully available in the community? Or does securing access to new technologies become part of the increasingly complex process of managing HIV prevention trials?

The FDA approval of PrEP for HIV prevention brings these issues into sharp focus. The provision of PrEP in populations with endemic HIV has the potential to prevent hundreds of thousands of HIV infections. This is highly unlikely to occur

through African health systems and established donor ARV programs in the immediate future, however, given current problems with sustaining ARV access for people who need these drugs to survive. If PrEP became ‘standard of prevention’ in trials, then HIV trial populations might become low incidence rather than high incidence populations, and this would add new levels of complexity to testing other prevention interventions. PrEP is hardly a “magic bullet”: it is a high-cost, high-maintenance strategy, requiring ongoing supplies of an expensive drug combination and daily adherence.

Could, or should, HIV prevention studies deliver costly prevention technologies like PrEP as ‘standard of prevention’? If so, the distinction between a research study and a prevention program or intervention becomes blurred, and the size and cost of trials would have to increase exponentially in order to be able to discern the benefit of any new intervention of top of the package. If not, then the question needs to be asked, for whom was PrEP developed, if not for populations at the greatest risk of HIV acquisition?

It is seductively easy to conclude that PrEP should be added to standard of prevention immediately. To do so however would be to ignore the role of host country regulators who have a valid stake in determining which interventions are prioritised in their countries, and at what cost. If PrEP is deemed too expensive by host country regulators, then the need for an affordable intervention, such as a vaccine or other long-acting technology, remains.

Finally, there are clear grounds to explore alternative trial models, such as innovative comparator studies that avoid placebos, in order to answer ‘real world’ questions, such as how PrEP measures up against other experimental prevention methods, whether that be new compounds or novel delivery systems of drugs already

in use. Ultimately, people at high risk of HIV acquisition need access to prevention interventions that are under their control, and low- and middle-income countries need data about which technologies perform best.

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References

Abdool Karim, Q., S. S. Abdool Karim, J. A. Frohlich, et al. 2010. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 329: 1168–1174.

Angell, M. 1997. The ethics of clinical research in the third world. *New England Journal of Medicine* 337(12): 847–849.

Ashcroft, R. E. 2004. Current epistemological problems in evidence based medicine. *Journal of Medical Ethics* 30(2): 131-135.

Auvert, B., D. Taljaard, E. Lagarde, J. Sobngwi-Tambekou, R. Sitta , A. Puren. 2005. 'Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial', *Public Library of Science (PLoS Med*.) 2005 Nov; vol. 2, no. 11: e298. Epub 2005 Oct 25.

AIDS Vaccine Advocacy Coalition. (AVAC). 2012. AVAC Urges FDA Approval of PrEP Following Positive Advisory Committee Recommendation; Lays out Priorities to Ensure Access. Thursday, May 10, 2012. Available at: http://www.avac.org/ht/display/ReleaseDetails/i/43963/pid/212c

[Accessed 14 May 2012**]**

Baeten, J. M., D.Donnell, P .Ndase, N. R. Mugo, J. D. Campbell, J. Wangisi, et al. 2012. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine* 367 (5):399-410.

Bailey, R. C., Moses, S., Parker, C. B., Agot, K., I. Maclean, J.N. Krieger, et al. 2007, 'Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial', *Lancet*, vol. 369, no. 9562 (February 24): 643-56.

Benatar, S.R., and P.A. Singer. 2000. A new look at international research ethics. *British Medical Journal* 321:824-6.

Boily, M.C., R. F. Baggaley, L. Wang, B. Masse, R.G. White, R.J. Hayes, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis* 9: 118-29, 2009.

Celum, C., and J. Baeten. 2012. Tenofovir-based pre-exposure prophylaxis for HIV prevention: evolving evidence. Current Opinion in Infectious Diseases: 25 (1):51–57 doi: 10.1097/QCO.0b013e32834ef5ef

Cohen, M. S., Y. Q. Chen, M. McCauley, T. Gamble, M. C. Hosseinipour, N. Kumarasamy, et al. 2011. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine* 365(6): 493-505.

Cohen, M.S., M. McCauley, and J. Sugarman, 2012. Establishing HIV treatment as prevention in the HIV Prevention Trials Network 052 randomized trial: an ethical odyssey. *Clinical Trials*, 2012. **9**(3): p. 340-347.

Compher, C. 2010. Efficacy vs Effectiveness. Journal of Parenteral and Enteral Nutrition. 34(6): 598-599.

Connor, E. M., R. S. Sperling, R. Gelber, P. Kiselev, G. Scott, M. O'Sullivan, et al. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus

type 1 with Zidovudine treatment. *New England Journal of Medicine* 331(18): 1173–1180.

Donnell, D. 2012. Changes in detectable plasma levels over time in a pre-exposure prophylaxis clinical trial: the Partners PrEP study. (Conference paper) Microbicides 2012, April 20 2012.

Feldblum, P. J., A. Adeiga, R. Bakare, S. Wevill, A. Lendvay, F. Obadaki, et al. 2008. SAVVY Vaginal Gel (C31G) for Prevention of HIV Infection: A Randomized Controlled Trial in Nigeria. *PLoS ONE* 3 (1):e1474.

Flynn, N.M., D.N. Forthal, C.D. Harro, K.H. Mayer, and M.F. Para (rgp120 HIV Vaccine Study Group). 2005. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *Journal of Infectious Diseases* 191: 654-665

Food and Drug Administration. (FDA). 2012. FDA Approves First Drug for Reducing the Risk of Sexually Acquired HIV Infection. (News release) July 16 2012. Silver Spring, MD: FDA. Available at:

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm [Accessed September 10, 2012]

Forbes, A., and S. Mudaliar. 2009. *Preventing Prevention Trial Failures: A Case Study and Lessons for Future Trials from the 2004 Tenofovir Trial in Cambodia*. Washington, DC: Global Campaign for Microbicides; 12. Available at: http://www.global-campaign.org/clientfiles/Cambodia.pdf [Accessed10 May 2012]

Freedman, B. 1987. Equipoise and the Ethics of Clinical Research. *New* England Journal of Medicine 317(3): 141-145.

Fried, Charles. 1974. Medical Experimentation: Personal Integrity and Social Policy. Amsterdam: North Holland.

Grant, R. M., J. R. Lama, P. Anderson, V. McMahan, A.Y. Liu, L. Vargas, et al. 2010. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine* 363(27): 2587–2599.

Gray R.H., Kigozi, G., Serwadda, D., Makumbi, F., S. Watya, F. Nalugoda, et al. 2007. 'Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial'. *The Lancet* 369, no. 9562 (February 24): pp. 657-66. http://www.proquest.com/ (accessed November 30, 2008).

Haire, B.G. 2011. Because we can: clashes of perspective over researcher obligation in the failed PrEP trials. *Developing World Bioethics.* 11(2): 63-74.

Heise L, Shapiro K, and West Slevin K. *Mapping the Standards of Care at Microbicide Clinical Trial Sites.* Washington, DC: Global Campaign for Microbicides; 2008.Available at: *http://www.global-campaign.org/clientfiles/SOC.pdf* [Accessed 14 May 2012]

Kippax, S. N. Stephenson 2012. Beyond the distinction between biomedical and social dimensions of HIV. *American Journal of Public Health*. 102 (5): 789-799.

Little M. "Better than numbers . . ." A gentle critique of evidence-based medicine. *Aust N Z J Surg* 2003; 73: 177-182.

Lurie, P. and S.M.Wolfe. 1997. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine* 337(12): 853–856.

McGrory, E., A. Irvin, L. Heise. *Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site. Washington, DC: Global Campaign for Microbicides at PATH; 2009. Available at: www.globalcampaign.org/clientfiles/Cameroon.pdf. Accessed: 8 January 2011.*

Macklin, R. Changing the Presumption: Providing ART to Vaccine Research Participants. *Am J Bioethics* 2006; 6: W1–W5.

Miller J and Glasner B. The "Inside" and the "Outside": Finding realities in interviews in D. Silverman (ed) *Qualitative Research: Theory, Method and Practice*. London: Sage, 2004: 125-129.

Miller, F.G. and S. Joffe, Equipoise and the Dilemma of Randomized Clinical Trials. *New England Journal of Medicine*, 2011. **364(**5): p. 476-480.

Padian, N. S., A. Buvé, J. Balkus, D. Serwadda, and W. Cates, Jr. 2008. Biomedical interventions to prevent HIV infection: Evidence, challenges, and way forward. *Lancet* 372 (9638): 585– 599.

Padian, N. S., A. van der Straten, G. Ramjee, T. Chipato, G. de Bruyn, K. Blanchard, et al. 2007. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. *Lancet* 370(9583): 251-261.

Page-Shafer, K., V. Saphonn, L. Sun, M.C. Vun, D.A. Cooper, and J.M., Kaldor. 2005. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. *Lancet* 366(9495): 1499-1503.

Peterson, L., D. Taylor, R. Roddy, et al. 2007. Tenofovir disoproxil rumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebocontrolled trial. *PLOS Clinical Trials* 2(5): e27.

Philpott, S., L. Heise, E. McGrory, L. Paxton, C. Hankins, and the participants in the GCM/CDC/UNAIDS Consultation on Standards of Prevention in HIV Prevention Trials. 2011. The challenge of defining standards of prevention in HIV prevention trials. *Journal of Medical Ethics* 37(4): 244-248.

Slack, C., M. Stobie, C. Milford, G. Lindegger, D. Wassenaar, A. Strode, et al. 2005. Provision of HIV treatment in HIV preventive vaccine trials: a developing country perspective. *Social Science & Medicine* 60(6): 1197–1208.

Rennie, S., J. Sugarman, and the HPTN Ethics Working Group. 2009. *HIV PreventionTrials Network ethics guidance for research*. HIV Prevention Trials Network. Available at: http://www.hptn.org/web%20documents/EWG/HPTNEthicsGuidance020310.pdf (accessed May 14, 2012).

Roehr, B. Tenofovir works as pre-exposure prophylaxis against HIV, two studies confirm 2011. *BMJ*. 343:d4540

rgp120 HIV Vaccine Study Group. 2005. *Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. rgp120 Vaccine Study Group.* J Infect Dis 191: 654-665.

The Review Team for NDA 21-752/S-30. 2012. Memorandum TRUVADA

(emtricitabine-tenofovir disoproxil fumarate). April 16, 2012. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM303213.pdf [Accessed 14 May 2012]

Thigpen, M.C., P.M. Kebaabetswe, L. A. Paxton, D. K. Smith, C. E. Rose, T. M. Segolodi,et al. *Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana.* New England Journal of Medicine, 2012. **367**(5): p. 423-434.

UNAIDS/WHO. 2000.(3rd reprint April 2004). Ethical considerations in HIV preventive vaccine research. UNAIDS Guidance Document. Geneva, Switzerland.

UNAIDS/WHO. 2007. *Ethical considerations in biomedical HIV prevention trials* [monograph]. Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at: http://data.unaids.org/pub/Report/2007/jc1399 ethicalconsiderationsen.pdf

Van Damme, L., G. Ramjee, M. Alary, et al. 2002. Effectiveness of COL-1492, nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: A randomised controlled trial. *Lancet* 360: 971–977.

Van Damme, L. 2010. Personal communication.

Van Damme, L., et al., *Preexposure Prophylaxis for HIV Infection among African Women.* New England Journal of Medicine, 2012. **367**(5): p. 411-422.

Varmus, H., and D. Satcher. 1997. Ethical complexities of conducting research in developing countries. *New England Journal of Medicine* 337(14): 1003–1005.

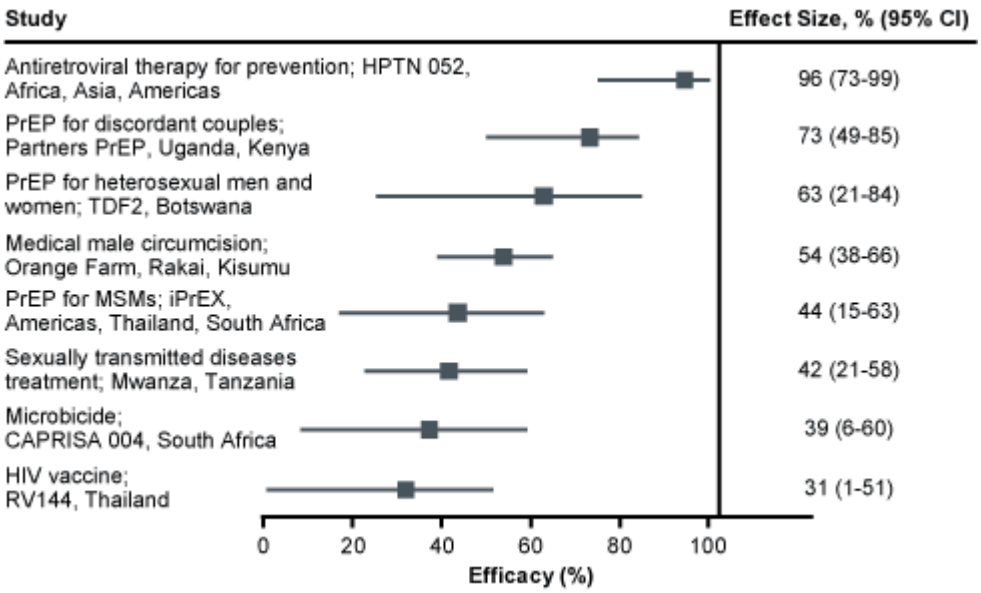
Worrall, J. 2002. What Evidence in Evidence - Based Medicine? *Philosophy of Science* 69(S3): S316-S330.

World Health Organisation. 2012 The 3 by 5 initiative: Treat three million people with HIV/AIDS by 2005. Originally published in 2003. Available at http://www.who.int/3by5/about/initiative/en/index.html [Accessed 1 November 2012]

World Medical Association. 2008. *Declaration of Helsinki*, amended. Originally published 1964.

Available at: http://www.wma.net/en/30publications/10policies/b3/index.html

Figure 1: Positive results of HIV prevention trials*



*The sexually transmitted diseases trial is not discussed in this article.

Source: S. McGregor, G. Tachedjian, B.Haire, J. Kaldor. The Seventh and Last International Microbicides Conference: From discovery to delivery. *Sexual Health* Inpress.

Part 2, Chapter 4

Mind the gap: An empirical study of post-trial access in HIV biomedical prevention trials

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Abstract

The principle of providing post-trial access for research participants to successful products of that research is widely accepted and has been enshrined in various declarations and guidelines. While recent ethical guidelines recognise that the responsibility to provide post-trial access extends to sponsors, regulators and government bodies as well as to researchers, it is the researchers who have the direct duty of care to participants. Researchers may thus need to act as advocates for trial participants, especially where government bodies, sponsors, and regulatory bodies have complex interests vested in decisions about whether or not new interventions are made available, how, and to whom. This paper provides an empirical account of post-trial access in the context of HIV prevention research. It describes both access to the successful products of research and the provision antiretroviral drugs for trial participants who acquire HIV. First, we provide evidence that, in the current system, there is considerable variation in the duration and timeliness of access. We then argue that by analysing the difficulties faced by researchers to this point, and their efforts to meet this obligation, much can be learned about how to secure post-trial access in HIV biomedical preventions trials. While researchers alone have a limited obligation, their advocacy on behalf of trial participants may be necessary to call the other parties to account.

Introduction

Providing research participants with post-trial access to successful interventions is required by key international ethical guidelines.[1] It is intended to protect research participants from exploitation, and to give trial populations an opportunity to benefit directly from research to which they contributed, where the research resulted in a successful product or intervention.[2] Post-trial obligations are particularly important for participants from lower income countries, where the obligations are linked to the principle that research conducted in lower income countries should be responsive to the health priorities of the country in which it is tested. Without these provisions, participants from lower income countries run the risk of being used to test

[1] World Medical Association (WMA). 1964, amended 2008. Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects;

Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002; Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO). 2012 (English original 2007, additional guidance point added 2012).UNAIDS/07.28E/JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS/WHO Guidance Document. Geneva: UNAIDS and World Health Organization. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf [Accessed 18 Feb 2013].

[2] D. Schroeder & E. Gefenas. Realising benefit sharing – The case of post-study obligations. *Bioethics* 2011; 26: 305-314.

interventions intended chiefly or solely for the benefit of populations in high income countries, because research in low incomes countries tends to be cheaper.[3]

The requirement to ensure post-trial access is complex, however. While investigators and research sponsors can provide access to interventions that are approved by regulatory bodies, they cannot supply unapproved medicines or interventions. Indeed, the term 'post trial' is in some respects misleading, as the key investigator-controlled method of supplying drugs for unapproved indications involves cross-over from placebo to active drug within trials, or clinical trial 'extension' mechanisms, and both mechanisms require regulatory and ethics approval. Investigators may thus undertake in good faith to supply any successful intervention to trial participants, but be stymied by regulatory authorities that deny or delay approval for extension-trial access. This raises two questions. First, how can trial investigators be required to deliver access to a product over which they have limited control? Second, what role should regulatory bodies and governments play?

The responsibility to facilitate post-trial access cannot rest on the investigator alone, as both CIOMS (2002) and the UNAIDS Ethical considerations in biomedical HIV prevention trials (2012) recognise.[4] The obligation is shared with sponsors, regulatory authorities, and other government bodies. This is logical, in that these bodies are essential to ensure timely access to newly validated interventions. It is also problematic, however, in that that government bodies and regulatory authorities have complex responsibilities when it comes to approving new medicine and interventions,

[3] R. Macklin. 2004. Double standards in medical research in developing countries. Cambridge, UK ; New York: Cambridge University Press.

[4] Op. Cit Note 1.

and they do not have the same direct duty of care to the research participant as a trial investigator.

Post-trial obligations also include arrangements to compensate participants for injuries or illness resulting from trial participation, and access to antiretrovirals (ARV) for participants in HIV prevention trials who acquire HIV during the trial (seroconverters). The basis for the obligation to supply ARV for seroconverters has been debated extensively.[5] Concerns about providing ARV access within trials were initially raised on the grounds that, if the trial were the only source of access, this could be seen to constitute an undue inducement,[6] and that it placed too great a burden upon research infrastructure.[7] Since ARV access programs have grown

[5] C. Slack, M. Stobie, C. Milford, G. Lindegger, D. Wassenaar, A. Strode & C. Ijsselmuiden. Provision of HIV treatment in HIV preventive vaccine trials: a developing country perspective. *Socl Sci Med* 2005; 60: 1197-1208; M.Merritt &C. Grady Reciprocity and post-trial access for participants in antiretroviral therapy trials. *AIDS* 2006; 20: 1791–1794; R. Macklin. Changing the Presumption: Providing ART to Vaccine Research Participants. *The American Journal of Bioethics* 2006; 6: 1 – 5; B. Lo, N. Padian & M. Barnes. The obligation to provide antiretroviral treatment in HIV prevention trials. *AIDS* 2007; 21: 1229-1231 10.1097/QAD.0b013e3281338371; J. Millum. Post-trial access to antiretrovirals: Who owes what to whom? *Bioethics* 2011; 25: 145-154; Op Cit note 2.

[6] I. de Zoysa., Elias, C. J., & Bentley, M. E. Ethical challenges in efficacy trials of vaginal microbicides for HIV prevention. *American Journal of Public Health 1998; 88*(4): 571-5; Kilmarx, P. H., Ramjee, G., Kitayaporn, D., & Kunasol, P.. Protection of human subjects' rights in HIV preventive clinical trials in Africa and Asia: Experiences and recommendations. AIDS, 2001; 15(supplement 4), S1–S7.

[7] D. Fitzgerald, , Pape, J. W., Wasserheit, J., Counts, G., & Corey, L. .Provision of treatment in HIV-1 vaccine trials in developing countries. Lancet, 2003; 362, 993–994.

exponentially, however, the debate now concerns the best mechanisms for delivery, rather than whether or not delivery is appropriate and/or feasible.[8]

The aim of this paper is to provide a comprehensive empirical account of post-trial access to successful interventions and ARV for seroconverters in the context of HIV prevention trials. We will analyse the efforts investigators say they make to vouchsafe post-trial access and the various outcomes achieved. We will also consider the procedural problems encountered in particular trials and the lessons that can be learned for planning future post-trial access provisions in order to inform future efforts for what is an ethically important endeavour.

Background – the HIV prevention context

In the last seven years, five different HIV prevention modalities have had positive results in nine clinical trials (Figure 1, Positive results of HIV prevention trials). The levels of relative risk reduction varied from a modest and contested 31% for a candidate vaccine[9] to an overwhelming and celebrated 96% for treatment-as prevention. [10] The evidence of efficacy for the various modalities is complex, with different trial populations showing varying levels of efficacy, and adherence emerging as a major problem in some of these populations.[11] Nevertheless, post-trial access

[8] Macklin Op. Cit note 5.

[9] S. Rerks-Ngarm, P. Pitisuttithum, S. Nitayaphan, et al. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *N Engl J Med* 2009; 361: 2209-2220. This figure is from the modified intent-to-treat analysis – the figure from the intent –to-treat analysis is 26%.

[10] M.S. Cohen, Y.Q. Chen, M. McCauley, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New Engl J Med* 2011; 365: 493-505.

[11] L. Van Damme, A. Corneli, K. Ahmed, et al. Preexposure Prophylaxis for HIV Infection among African Women. *New Engl J Med* 2012; 367: 411-422; J.M. Baeten, D. Donnell, P. Ndase, et al.

provisions for participants in HIV prevention trials need to be examined in light of these results. It is also important to discuss how, in the case of each different product, post-trial access conditions have been met, and identify the barriers to access.

Prior to the prevention trials described above, biomedical HIV prevention interventions designed to prevent sexual transmission of HIV (as opposed to mother-to-child, or 'vertical' transmission) had been unsuccessful. Indeed, the vaginal microbicide nonoxynol-9 was found to increase the risk of HIV acquisition.[12] A subsequent product, cellulose sulphate also showed a trend toward enhancing transmission, though it did not reach statistical significance.[13] Other investigational microbicide products also showed trends towards increasing risk.[14] Further, an investigational HIV vaccine trial in 2007 was also prematurely halted, again because

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Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine* 2012; 367: 399-410.

[12] L. Van Damme, G. Ramjee, M. Alary, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *The Lancet* 2002; 360: 971-977.

[13] L. Van Damme, R. Govinden, F.M. Mirembe, et al. Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission. *N Engl J Med* 2008; 359: 463-472.

[14] P.J. Feldblum, A. Adeiga, R. Bakare, et al. SAVVY Vaginal Gel (C31G) for Prevention of HIV Infection: A Randomized Controlled Trial in Nigeria. *PLoS ONE* 2008; 3: e1474; A. Nunn, S. McCormack, A. Crook, R. Pool, C. Rutterford & R. Hayes. Microbicides Development Programme: design of a phase III trial to measure the efficacy of the vaginal microbicide PRO 2000/5 for HIV prevention. *Trials* 2009; 10: 99. In this latter study, the 2% Pro 2000study arm was discontinued but the 0.5 % arm continued.

it enhanced transmission, in this instance in the sub-population of uncircumcised men.[15]

During this period of HIV prevention research, which began with the oral reporting of the nonoxynol-9 results at the Durban International AIDS Conference in 2000, 'post-trial access' debates focussed on access to antiretrovirals (ARV) for trial participants who became HIV positive (seroconverted) during prevention trials, and ongoing provision of medical care for trial-related medical conditions. Accordingly, we will adopt a broad definition of post-trial access to include ARV access for seroconverters and access to successful products from clinical trials.

The treatment access movement

The efficacy of antiretroviral drugs in the treatment of HIV was established in 1996, but initial access was predominantly limited to high-income countries and elites within lower income countries. Consequently, countries that were suitable sites for HIV prevention trials because of their high HIV incidence frequently lacked both the health budget and the infrastructure to provide ARV. Access to ARV for people who seroconverted during trials in countries where there were no general ARV programmes was thus a fraught issue both logistically and ethically.

The treatment access movement, spearheaded by Treatment Access Campaign in South Africa and various ACT-UP chapters elsewhere, gained significant momentum

[15] S.P. Buchbinder, D.V. Mehrotra, A. Duerr, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet* 2008; 372: 1881-1893. G.Gray, S Buchbinder and Ann Duerr. Overview of STEP and Phambili trial results: two phase IIb test of concept studies investigating the efficacy of MRK ad5 gag/pol/nef sub-type B HIV vaccine. *Curr OpinHIV AIDS* 2010; 5: 357-361.

in early 2000.[16] Drug discounting, the rise of generic ARV, and the UNAIDS/WHO initiative '3 by 5' (an action plan to supply ARV to three million people living with HIV by 2005) were major drivers of this momentum. Importantly, the '3 by 5' initiative took a public health approach, simplifying and standardising ARV regimens[17] with a focus on minimising infrastructural requirements to improve the feasibility of ARV in resource-limited environments.

The other great enabler of ARV access in lower income countries was the establishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002, and the President's Emergency Fund for AIDS Relief (PEPFAR) in 2003. Of the eight million people worldwide on ARV in 2011, the vast majority were funded through the Global fund or PEPFAR.[18]

Prevention of vertical (mother-to-child) transmission

Programs to prevent vertical transmission in lower income countries have evolved considerably in the last decade. Key changes in recommendations from the World Health Organization in 2010 included earlier access to ARV in pregnancy, longer

[16] M. Heywood. South Africa's Treatment Action Campaign: Combining Law and Social Mobilization to Realize the Right to Health. *Journal of Human Rights Practice* 2009; 1: 14-36.

[17] There are some down-sides to this, such as the ongoing use of the now-supplanted drug, d4T or stavudine, in many low-income countries. This drug while effective has a very problematic side effect profile.

[18] In point of fact, the estimates provided on the PEPFAR and Global Fund websites exceed the total number of people worldwide estimated by UNAIDS to be accessing ARV. Available at: http://www.theglobalfund.org/en/about/whoweare/ http://www.pepfar.gov/funding/results/index.htm [Accessed 7 March 2013]

provision of ARV to women with relatively healthy immune systems[19], and provision of ARV to the mother or child during breastfeeding (WHO 2010).[20] Treatment regimens also changed. Single dose nevirapine, an antiretroviral drug which reduced transmission but caused option-limiting maternal drug resistance, was no longer recommended as a stand-alone prophylaxis, but was recommended in combination with other drugs to further suppress viral replication and prevent drug resistance (Option A).[21] Fully suppressive triple combination therapy throughout pregnancy and breastfeeding (Option B) was recommended where feasible. These interventions are intended to reduce HIV transmission to less than 5 percent in breastfeeding populations, and less than 2 percent in non-breastfeeding populations.

In April 2012, a further update on pregnancy guidelines was introduced with an 'Option B+', which differed from Option B in that the maternal treatment would be a life-long a universal triple combination ARV regimen, as distinct from one that ends

[19] 'Relatively healthy immune systems' in this context means women with CD4 cell counts of over 350. In 2010, people with CD4 cell counts above this level were assessed to not need ARV for their own health (but might require ARV as prophylaxis in pregnancy). Subsequent trial data, while not definitive, now suggests health benefits of earlier treatment. (Cohen et al. 2011; The SPARTAC Trial Investigators 2013, Le et al.. 2013)

[20] World Health Organisation. 2010. New guidance on prevention of mother-to-child transmission of HIV and infant feeding in the context of HIV. Available at: http://www.who.int/hiv/pub/mtct/PMTCTfactsheet/en/index.html

[21] The regimen known as WHO 'Option A' is maternal AZT from 14 weeks if possible, single dose nevirapine plus AZT/3TC during birth, then AZT/3CT for seven days post partum, with breastfeeding infants taking nevirapine until seven days after weaning. Prophylaxis for non-breastfeeding infants is nevirpine or single dose nevirapine plus AZT for 4-6 weeks for Option A. WHO 'Option B' is an effective triple combination therapy with infant post-exposure prophylaxis of nevirapine or AZT for 4-6 weeks.

at weaning. The purpose of the B+ option is to optimise care for HIV positive women in the light of evidence that stopping and restarting therapy may be detrimental, better treatment outcomes may proceed from earlier ARV initiation, and ARV treatment has a preventative aspect for sexual partners. [22]

Importantly, WHO guidelines recommend that national HIV programs in southern Africa implement within different timeframes, according both to resourcing issues and political will. For instance, Malawi is the only low income country to date to introduce Option B+ as policy.[23] In southern African countries that hosted the HIV prevention trials discussed above (Figure 1), there were different national standards of care for ARV access, and they sometimes changed during those trials.[24] In addition, WHO guidance and even national guidelines can be 'aspirational' rather than actually implemented in some countries.[25] Thus the standard of care implemented at a local level may differ from national guidelines,[26] and rigorous implementation of national guidelines in such a setting would therefore improve the standard of care available.

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[22] World Health Organization. 2012. Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Available at: http://www.who.int/hiv/PMTCT_update.pdf [Accessed 6 March 2013]

[23] Schouten E.J., A. Jahn, D. Midiani, et al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. *Lancet* 2011; 378: 282–84.

[24] M.S. Cohen, M. McCauley & J. Sugarman. Establishing HIV treatment as prevention in the HIV Prevention Trials Network 052 randomized trial: an ethical odyssey. *Clinical Trials* 2012; 9: 340-347.

[25] ibid

[26] A.J. London. The Ambiguity and the Exigency: Clarifying 'Standard of Care' Arguments in International Research. *J Med Philos* 2000; 25: 379-397

We will focus on the investigator role in post-trial access, and provide an empirical account of how the issue has played out in HIV prevention trials with successful interventions, along with accounts of ARV treatment access for seroconverters (including those who were pregnant). We will describe the variations in both the timelines and duration of access to successful interventions and discuss how regulatory authorities and other government bodies can face multiple conflicts of interests when it comes to ensuring access to particular interventions.

Methods

Empirical data are drawn from HIV prevention trial websites, published literature, email exchanges with principal investigators of HIV prevention trials and semi-structured interviews with principal investigators who conducted biomedical HIV prevention trials for sexual exposure between 2000 and 2011 that had positive findings. This is part of a larger qualitative study on standards of care in HIV prevention trials.

Twenty-eight efficacy trials of biomedical HIV prevention (either phase III or IIb) were identified between 2000 and 2011 through the Current Controlled Trials and clinical trials.gov databases. Of these, nine had positive findings. Principal investigators (PIs) and first authors of key publications were contacted by email and invited to participate in the study by participating in a semi-structured interview. Each was sent at least one follow-up interview request email.

The interviews were conducted from May 2010 to March 2012, a period during which five of the nine successful HIV biomedical prevention trials had positive findings (CAPRISA 004, iPrEX, HPTN 052, Partners PrEP and TDF-2). In several cases, the positive trial results were known by the informant but not by the interviewer.

All of the interviews were conducted by the first author. Three interviews were conducted by telephone and one was face-to-face. The study was reviewed and approved by the ethics committee of the University of Sydney. Data was coded using N-Vivo 9 software and analysed thematically.

Where interview data were factual (as distinct an expression of an opinion), facts were verified against other sources, such as trial protocols. Principal investigators (PI) of HIV prevention trials with positive findings were contacted by emails for fact-checking and to supply additional information. This group included PIs who had not been interviewed. In instances where PIs had been interviewed, specific permission was requested and granted to use some quotes from interviews in a manner that might allow identification. In one instance the PI referred the authors to another senior member of the research team to supply further details.

PIs who were not interviewed were engaged in email exchanges on post-trial access issues. Of the nine positive trials, two PIs did not respond either to requests for an interview or to provide email comments. In these case (the RV144 vaccine trial and the Orange Farm circumcision trial), information about post-trial access plans was sourced from publications, pre-trial documents and post-trial access meeting minutes provided by AVAC (AIDS Vaccine Advocacy Coalition) and by an RV144 trial-related public relations officer.

Personal communications were re-checked for accuracy with the PIs who made the comments.

Results

Four of the nine PIs responded to requests for interviews. Of the remaining 5 PIs, three engaged in email exchanges explaining and clarifying aspects of the post-trial access. The PIs interviewed also provided clarifications and further information through email exchanges. Two did not respond.

Access to successful products in the positive trials

In trials of the five biomedical HIV prevention modalities that were shown to significantly reduce the risk of infection, there was an arrangement in place to ensure access to successful interventions for trial participants. Eight of the nine trials were obliged to provide access to a product for participants, as one of the pre-trial agreements specified an efficacy threshold that was not reached.

Following is an account of the post-trial access provided by each trial.

HPTN 052

The landmark HPTN052 study tested the proposition that treating people with HIV could have a preventive benefit for their partners. It was conducted in 1763 serodiscordant couples, with the HIV positive (or 'index' partner) randomised either to receive immediate ARV, or to delay treatment until such time as his or her CD4 cell counts fell to 350 or below. The study was projected to run for five years, with an agreement in place for people on the delayed treatment arm to be switched to immediate treatment once if immediate treatment showed an HIV prevention benefit

(an 'intra-trial' access provision rather than a post-trial access). The trial released results when it had be running for less than two years, upon advice from the Data Safety Monitoring Board. All participants on the delayed arm were offered immediate treatment, though the study would continue until May 2014.[27]

Most, though not all, participants on the delayed therapy arm took advantage of the offer to switch to immediate therapy, and many of those who did not do so initially in 2011 are now doing so.[28] Post-trial access proper will commence at the end of the study in 2015. Each trial site has an access plan, which is about transitioning participants from trial-supplied ARV to locally provided ARV.[29]

CAPRISA 004

The CAPRISA 004 IIb study tested a 1% tenofovir gel as a vaginal microbicide, using a very specific dosing regimen with doses before and after sex, with no more than two doses in a 24 hour period. While the CAPRISA 004 trial produced a positive result with a relative risk reduction of 39%,[30] the statistical power of the study was deemed insufficient for licensure.[31] Despite the 004 investigators having secured access to the

[27] M.S. Cohen,Y.Q. Chen, M. McCauley, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New Engl J Med* 2011; 365: 493-505.

[28] Marybeth McCauley, senior member of the HPTN research team, personal email communication

[29] ibid

[30] Q. Abdool Karim, , S. S. Abdool Karim, J. A. Frohlich, et al. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 2010; 329: 1168-1174.

[31] UNAIDS. 2010. Road-map agreed for confirmatory trials of promising microbicide. Geneva. Available at: http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2010/september/20100903prcaprisa [Accessed 5 March, 2013]

patent for the product in Southern Africa where the trial took place, [32]participants of CAPRISA 004 faced a 24-month delay between the end of the initial study and the commencement of a roll-over study, CAPRISA 008. At the time of writing, past CAPRISA 004 participants can enrol in this open label study, which compares accessing tenofovir gel through trial site mechanisms to accessing it through family planning providers. The study investigators intended that participants from other HIV prevention studies and volunteers from the communities where the trial took place (as per UNAIDS Guidance point 19) should be able to join the 008 study, but regulatory approval for this was not secured at the time of writing.[33]

PrEP trials: iPrEX, Partners PrEP and TDF-2

The three positive PrEP trials provided access to PrEP products (TDF/FTC, or TDF alone) to participants through extension studies, which operated slightly differently to each other.

Partners PrEP tested two different PrEP regimens, tenofovir alone and tenofovir/emtricitabine combined as a single tablet (TDF/FTC) in a population of 4758 serodiscordant heterosexual couples in Kenya and Uganda. The HIV positive partner in each of the couple was not yet eligible for ARV under national guidelines.

[32] Press release. Terms of deal to make gel affordable and accessible in Africa following regulatory approval. *Eureka Alert* 2010. Available at: http://www.hst.org.za/news/next-steps-tenofovir-gel-conrad-and-tia-sign-license-agreement [Accessed 5 March, 2013]

[33] Centre for the AIDS Programme of Research in South Africa (CAPRISA). CAPRISA 008 MCC Correspondence: Sequence of Events; Q. Abdool Karim, S.S Abdool Karim & L. Mansoor. Letter to Dr Portia Nkambule, Medicines Control Council. 22 March 2012.

The trial found that tenofovir PrEP showed a relative reduction in HIV acquisition of 67%, while for TDF/FTC it was 75%.[34]

Once these results were released, access to active PrEP for participants on placebo was achieved through an amendment of the existing protocol to randomise participants from the placebo arm to 12 months of PrEP (either TDF/FTC or TDF alone) through an extension within the study protocol.[35] Participants already randomised to either TDF or TDF/FTC continued to receive their assigned treatment for that additional 12 month period.[36]

The ethical justification for continuing to randomize to the two different PrEP arms was that the difference in efficacy between the two active arms, TDF alone (67%) and TDF/FTC (75%) was not statistically significant. TDF alone is a cheaper option, so extra data on the comparison between the two was of significant public health importance.[37]

TDF-2 tested combined TDF/FTC in a population of 1219 heterosexual men and women in Botswana. It found that TDF/FTC reduced the relative risk of HIV acquisition by 62%. Once the results were released, TDF/FTC was supplied to all participants who wanted it post-trial through a 12-month open-label extension study.[38]

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[34] J. M. Baeten., D. Donnell, P. Ndase, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New Engl J Med* 2012; 367: 399-410.

[35] Protocol Addendum #8, 28 July 2011. Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV -1 Acquisition within HIV-1 Discordant Couples. Version 3.0, 12 October 2007 p 2.

[36] ibid

[37] Ibid; J. Beaten, personal email communication, 14 January 2013.

[38] M. Thigpen, personal email communication, 25 January 2013.

There was however a gap of 12 months from the time that the study results were released to the time that the extension study began.[39]

iPrEx tested combined TDF/FTC in a population of 2499 men and transgendered women who have sex with men in Peru, Ecuador, Brazil, the US, Thailand and South Africa. It found that TDF/FTC reduced the relative risk of HIV acquisition by 44%.[40] Subsequent data analysis has shown higher levels of efficacy related to better adherence to the drug (Anderson et al. 2012).[41] Post-trial access for iPrEX participants (both placebo and active drug arm participants) was through a 72-week open label extension study, which began three months after iPrEx stopped.[42]

[39] AVAC. ARV-Based Prevention Options Timeline Available at: http://www.avac.org/ht/a/GetDocumentAction/i/46212 Accessed 5 March 2013.

[40] R.M. Grant, J.R. Lama, P.L. Anderson, et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. New Engl J Med. 2010; 363: 2587-2599.

[41] P. L. Anderson, D.V. Glidden, A. Liu, et al. Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men. *Science Translational Medicine* 2012; 4; Anderson P, Liu A, Buchbinder S, et al.; the iPrEx Study Team. Intracellular tenofovir-DP concentrations associated with PrEP efficacy in MSM from iPrEx. Presented at: 19th Conference on Retroviruses and Opportunistic Infections; March 2012; Seattle, Washington.

[42] AVAC. Op. Cit. Note 33.

Circumcision trials

In the three randomized controlled trial of circumcision, participants in the control arm were able to access circumcision through trial mechanisms at the end of the follow-up period (i.e. once the trials were stopped by their respective Data Safety Monitoring Boards due to evidence of efficacy). In the Orange Farm (South Africa) trial, circumcisions were performed by contracted local practitioners, while in the Kenya trial, they were performed by trial doctors. In Rakai, Kenya, the circumcisions were performed by trial trained and certified physicians in well-equipped operating theatres'.

The Orange Farm trial was followed by an implementation trial, The ANRS 12126 "Bophelo Pele" project (Lissouba et al. 2010),[43] which was intended demonstrate the feasibility of MMC in 'real life' settings.

Vaccine trial RV 144

The Thai ALVAC/AIDSVAX vaccine tested two vaccines in a prime and boost regimen (six vaccinations in all), in a population of 16,402 Thai people (participants were not at increased risk of HIV). The trial reported a modest positive result (31.2%) in September 2009. This result reached statistical significance on only one of three key statistical analyses (the reported result was the modified intent-to-treat analysis, while both the intent-to-treat and per-protocol analyses did not reach statistical

[43] P. Lissouba, D. Taljaard, D. Rech, et al. A Model for the Roll-Out of Comprehensive Adult Male Circumcision Services in African Low-Income Settings of High HIV Incidence: The ANRS 12126 Bophelo Pele Project. *PLoS Med* 2010; 7: e1000309.

significance and showed a lower relative risk reduction of around 26%). Thus there remains a higher possibility that the reduction in HIV acquisition was due to chance than in the other positive prevention studies. In addition, the vaccines' efficacy appeared to wane over time, and was more effective in people at lower risk of HIV rather than those at higher risk.[44]

It was predetermined that placebo recipients in the trial would be offered the active vaccine if it were 50% or more effective (RV 144 meeting report March 16-18),[45] which is also the threshold for licensure in Thailand. There is however no evidence that the affected communities were involved in setting this threshold.[46] This decision regarding placebo recipients was re-examined at a meeting of international experts in March 2010. Reasons cited against provision of the vaccines for placebo recipients were:

- The low level of efficacy and wide confidence intervals (ranging from 1% to 52%);
- The vaccine regimen did not reduce viral burden in the volunteers who became infected with HIV following vaccination;
- The possibility of behavioural disinhibition (increased risk-taking) counteracting any biological efficacy; and

[44] S. Rerks-Ngarm, P. Pitisuttithum, S. Nitayaphan, et al. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *N Engl J Med* 2009; 361: 2209-2220.

[45]C. Hankins, R Macklin, N Michael, D. Stablein and participants. Meeting Report. Recommendations for the Future Utility of the RV144 Vaccines to the Thai Ministry of Health. March 16-18, 2010.

[46] Ibid.

- Provision of active vaccine to placebo recipients could compromise their participation in subsequent vaccine studies.

Thus the group recommended that there was no obligation at this point in time to offer the RV144 vaccine regimen to the placebo group in the trial.[47]

In a similar vein, the meeting decided that the use of placebos in further vaccine trials remains appropriate, and that RV 144 vaccines should not be added to the standard of prevention in other trials. On the other hand the group also decided that volunteers who were in the placebo group for the RV144 trial should be given priority in the future for access to the RV144 vaccine regimen, or new iterations of the RV144 vaccine regimen.[48]

Participants who acquired HIV on the trial (from both active vaccines and placebo arms) were eligible for the RV 152 follow-on study, looking at viral dynamics. A small number of participants who had received active vaccine and remained HIV negative were eligible for a follow-on study that re-boosted vaccine levels (RV 306).[49]

One PI, for whom access to successful products was very important, summed the issue up thus:

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[47] Ibid

[48] Ibid

[49] IAVI. Understanding Vaccine Licensure What factors do regulatory bodies consider before licensing a vaccine for public use? Vax 2009; 7 (12).

Available at: http://www.vaxreport.org/Back-Issues/Pages/UnderstandingVaccineLicensure.aspx

[Accessed 7 March 2013].

I think that whenever we asked people or communities to support a clinical trial or new intervention, we are asking them to believe that at some point in the future, if the trial shows that it's safe and effective, that intervention will become available. And I don't think that anyone necessarily expects the trial itself to guarantee future access to therapies that are found to be effective in the trials. But there has to be the belief that they will become available through the concerted efforts of the scientists and the public health community and government leaders and community stakeholders – there has to be a faith that what we learn from these studies will actually become available. And if you're working in an environment where therapies that are known to be beneficial are not yet available, it strains credibility. (PI interview, August 2011)

Provision of ARV in the positive trials

In all of the trials with positive results, ARV access was available to seroconverters, with some variations as to how this was achieved:

- CAPRISA 004 sites had ARV treatment programs and were not reliant on referrals to other facilities, with ARV available according to national guidelines[50];

- HPTN 052: HIV negative partners who seroconverted were released from the study and referred to a prearranged local clinic for care according to national guidelines. Any woman who was pregnant at enrolment or became pregnant was provided antiretroviral therapy appropriate for use during pregnancy at the start of the second trimester. On the basis of the judgment of the site

[50] Principal Investigator interview, June 2010.

investigator, women in the delayed-therapy group discontinued antiretroviral therapy after delivery or when breast-feeding ended.[51] (Cohen et al. 2011)

- HIV positive participants[52] from the Orange Farm (South Africa) circumcision trial accessed ARV through a specific program at the Voluntary Testing and Counselling centre, which was to remain in place until the public sector programme became operational in the area;[53]

- Seroconverters from the Kisumu (Kenya) circumcision trial were referred to the project's post-test counselling and support group and provided access to free HIV treatment and care;[54]

- Seroconverters in the Rakai (Uganda) trial were referred to a PEPFAR-funded HIV treatment programme. Those who were eligible for antiretroviral therapy (CD4 cell count less than 250 or WHO advanced stage III or stage IV disease) and who agreed to receive care were provided with antiretrovirals;[55]

[51] Cohen et al. op cit. Note 21

[52] This trial enrolled both HIV positive and HIV negative men. Men who were HIV positive at baseline were excluded from the statistical analysis. B. Auvert,, D. Taljaard, E. Lagarde, et al. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLoS Med* 2005; 2: e298.

[53] ibid.

[54] R. Bailey, S. Moses, C. Parker, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; 369: 643 - 656.

[55] R. Gray, G. Kigozi, D. Serwadda, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; 369: 657 - 666.

- Partners who had HIV in PP: Those who became eligible for the initiation of antiretroviral therapy according to national guidelines were actively counselled to initiate treatment and referred to local clinics;[56]

- Vaccine trial RV 144: Volunteers who acquired HIV infection during the trial were given free access to HIV care and treatment, including highly active antiretroviral therapy (HAART), according to the guidelines of the Thai Ministry of Public Health. Seroconverters were also offered extended follow-up in a separate study (RV152).[57]

Discussion

Each of the nine positive HIV prevention trials had done some kind of access planning in the event that their trial produced an effective intervention, and each had provisions for access to ARV for seroconverters. This suggests that post-trial access is considered normative. Differences were evident however in the mechanisms for providing access, the timeframes in which this was achieved, and the length of time for which it was sustained.

Product-dependent feasibility

The nature of the prevention modality affects the ease with which access can be provided. Access to male circumcision, for example, is achievable at a practical level because it requires a single intervention (plus healing time and follow-up as

[56] Baeten et al. Op cit note 28

[57] US Military HIV Research program. RV152: A Follow-up Study for RV144. Available at: http://www.hivresearch.org/media/pnc/9/media.549.pdf [Accessed 6 March 2013].

required).[58] Vaccines too have this advantage, and even though the Thai ALVAC/AIDSVax required an unusually high number of vaccinations – six – this a finite number rather than an ongoing program (of note the number of vaccinations ma be increased in subsequent trials – website)[59].

Interventions that require ongoing use are far more complex to supply, as is the case with tenofovir gel, PrEP (either tenofovir alone or TDF/FTC) and treatment-as-prevention. While PrEP has US FDA approval, it has not been approved in the other eight countries in which it was trialled (South Africa, Kenya, Uganda, Ecuador, Brazil, Peru, Thailand, Botswana). Demonstration sites (access programs that also collect further data) are being organised in the US and several cities in Brazil (Brazil requires post-trial access by law).[60]

Provider-dependant safety/efficacy

Of note in the three circumcision studies, there was a lower incidence of adverse effects in the Kisumu trials compared with Orange Farm (1.5% compared with 3.6%).[61] This was attributed to the use of trial doctors rather than contracting local practitioners, as occurred in Orange Farm. In the Rakai trial physicians were trained

[58] Campaigns against circumcision, such as that waged by the Ugandan president, obviously have a negative impact on its achievability.

[59] RV144 Follow-up Study RV305 Begins in Thailand. November 4 2012. Available at: http://www.hivresearch.org/news.php?NewsID=238 [Accessed 6 March 2013].

[60] Track C Session summary TUWS02, Implementing Pre-exposure Prophylaxis: Current Progress and Future Challenges. AIDS 2012. Available at: http://rapporteurs.aids2012.org/SummaryView.aspx?summary_id=187 Accessed 6 March 2013.

[61] Bailey et al. op. cit note p 653

to perform the circumcisions, but subsequently the investigators showed that clinical officers (roughly equivalent to physicians' assistants) could perform the surgery safely.[62]

The gaps

Despite the considerable commitment to post-trial access displayed by the CAPRISA 004 investigators in securing the patent to tenofovir gel for southern Africa, participants waited more than two years between the end of that trial and the beginning of CAPRISA 008, which would provide open label access to tenofovir gel.[63] The delay was due to regulatory processes. The first iteration of the CAPRISA 008 trial was submitted in November 2010, within four months of the trial results being released. The trial did not begin enrolment until November 2012, however, due to protracted negotiations over the protocol and a series of newly imposed requirements from the regulator.[64]

As the CAPRISA 004 participants on the placebo arm had an HIV incidence of 9% during that trial, [65] an estimated 134 of the 745 women eligible for the 008 trial might be expected to seroconvert within the two years that elapsed between the end of 004 and the beginning of 008 (prior to 004 the HIV incidence in the CAPRISA 004 population was 15.6 % in the urban site and 11.2% in the rural).

The TDF 2 trial had a gap of 12 months before the end of the trial proper and the commencement of the open label extension trial, attributed to delays in the ethics

[62] R. Gray, personal email communication, 8 January 2013.

[63] CAPRISA 008 is an open-label study, with participants randomised to receive the gel either through trial-type settings or through family planning clinics.

[64] Q. Abdool Karim, SS Abdool Karim, L. Mansoor. *op cit* note 27

[65] Abdool Karim et al. *op cit* note 24

approval process, and concerns from the Ministry of Health that the extension study could be confused with government policy.[66] The iPrEx trial had a gap of three months. The Partners PrEP study however had virtually no gap,[67] which the principal investigator attributed to the access mechanism being an addendum to the trial rather than a separate access study.[68]

ARV access

Elevating the standard: pregnancy

Both HPTN 052 and Partners PrEP provided pregnant women with HIV with a higher standard of care than the national guidelines (whether the women seroconverted on the study, or in the case of HPTN, women who already had HIV but were on the delayed treatment arm). Pregnant HIV positive women – and breast feeding women who seronverted in Partners PrEP – were initiated on triple combination ARV therapy to minimise the risk of infant infection. WHO guidelines have now moved toward recommending this level of treatment for women in lower income countries more generally and continuing it indefinitely rather than stopping treatment after weaning (the B+ option), but at the time of these trials, lower standards such as single or dual therapies were in place.[69]

[66] Michael Thigpen, personal email communication, 13 January 2013.

[67] AVAC. Op cit note 33.

[68] Baeten. Op cit note 31

[69] World Health Organisation. Summary of new recommendations: When to start ART in people with HIV. Available at:

This is an example of researchers taking an opportunity to maximise a benefit to particular participants at a time when the stakes are high (the infant is at risk) and the participant is vulnerable (having just acquired HIV). Triple combination therapy reduces HIV acquisition to below 2%,[70] and does not carry the same risk of subsequent drug resistance as single or dual therapy for the mother once therapy is ceased. Provision of triple therapy in pregnancy/breastfeeding is unlikely to be too burdensome, in that it is time limited, and only a small number of women within a trial would both become pregnant and acquire HIV, but the intervention is grounded in sound evidence, feasible within the trial context, and of incalculable value to the women who were thus able to provide additional protection for their infants.

Of note in HPTN 052, participants who seroconverted during the trial and did *not* become pregnant accessed ARV through local programs operating within national guidelines. As seroconversion signalled an end to trial participation, these seroconverters were not able to avail themselves of the early treatment option when the results were released and early treatment supplied to those initially allocated to the delayed treatment arm. So while all HPTN 052 participants had treatment options at least equal to the national standard, those who seroconverted during the study did not have the same options as those who were HIV positive at entry, or those who became pregnant.

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http://www.who.int/hiv/pub/guidelines/arv2013/intro/summarynewrecommendations.pdf [Accessed 27 August 2013].

[70] E.R.Cooper, M. Charurat, L. Mofenson, et al. Combination Antiretroviral Strategies for the Treatment of Pregnant HIV-1-Infected Women and Prevention of Perinatal HIV-1 Transmission. *JAIDS* 2002; 29: 484-494.

How good is good enough?

Both the CAPRISA 004 result and the Thai RV 144 vaccine warrant discussion of the levels of efficacy required before access to participants is required.

The predetermined threshold of 50% relative risk reduction before access in RV 144 is a high one, and one that was apparently set by researchers and sponsors without community input. [71]At an international meeting of experts in 2009, views about the level of efficacy required for an intervention to be considered a valuable public health tool ranged between 20-80 percent, with most views falling between 30-50% .[72] Mathematical models have shown public health benefits of prevention interventions with only 30% relative risk reduction.[73] However, the fact that the relative risk reduction appeared to decrease over time and that people at higher risk seemed less protected than those at lower risk, mitigate against arguments for access either for participants or more broadly. While there appears to be some scientific basis for believing that the vaccines did indeed induce an immune response that had marginal efficacy in some participants,[74] the question of whether or not these participants were truly exposed to HIV at infectious levels remains unanswerable. Together with the

[71] Hankins et al. *op cit* note 39.

[72] R. Macklin. Ethical challenges in HIV microbicide research: What protections do women need? *International Journal of Feminist Approaches to Bioethics* 2011; 4: 124-142, 128.

[73] J.M. Kaldor, & D.P. Wilson. How low can you go: the impact of a modestly effective HIV vaccine compared with male circumcision. *AIDS* 2010; 24: 2573-2578 10.1097/QAD.0b013e32833ead96.

[74] G. Pantaleo, M. Esteban, B. Jacobs & J. Tartaglia. Poxvirus vector-based HIV vaccines. *Current Opinion in HIV and AIDS* 2010; 5: 391-396 10.1097/COH.0b013e32833d1e87.

issues of statistical significance,[75] this adds up to the reasonable conclusion that the RV 144 vaccines are a poor prospect for public health right now, though a rich source of hypotheses for further vaccine trials.

CAPRISA 004 is rather different. Tenofovir gel is a user-dependent technology, unlike a vaccine. A vaccine trial gives a fairly straightforward account of biological efficacy, but with a user dependent technology the question 'was it used?' is integral to working out whether it worked. Quantifying adherence is essential to sorting out efficacy, and the high adherers – those who adhered to the gel dosing schedule 80% or more of the time – had a relative risk reduction of 54%, while the incidence reduction in low adherers (less than 50% adherence) was 28%.[76] The adherence issue with a user-dependent technologies means that modest results in trials may be an indication of failure to use the product rather than the product itself being only modestly effective.[77]

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[75] P.B.Gilbert, J.O. Berger, D. Stablein, et al. Statistical Interpretation of the RV144 HIV Vaccine Efficacy Trial in Thailand: A Case Study for Statistical Issues in Efficacy Trials. *Journal of Infectious Diseases* 2011; 203: 969-975.

[76] Abdool Karim et al. op cit note 24

[77] The VOICE results, released on March 4 2013, are an excellent case-in-point. Despite the biological efficacy of interventions such as tenofovir/emtricitabine PrEP, this intervention had no effect on HIV transmission in a non-adherent population. J. Marrazzo., G Ramjee, G Nair, et al. *Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine or vaginal tenofovir gel in the VOICE study (MTN 003).* 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 26LB, 2013.

Despite relative risk reduction of more than 50% in high adherers and an overall reduction of 39%, the CAPRISA 004 trial was a relatively small trial (889 participants) had wide confidence intervals of 6-60%, meaning in the worse case scenario it is possible that the relative risk reduction gel produced was as low as 6 %. Accordingly, both South Africa's Medicines Control Council (MCC) and the USA's Food and Drug Administration (FDA) ruled that a confirmatory trial or trials would be required for licensure.

The VOICE trial (MTN003) tested three difference active arms – tenofovir gel, tenofovir oral PrEP and TDF/FTC combined oral PrEP – against matched placebos. Although VOICE had already begun, the FDA decided that data from the tenofovir gel arm of this trial, when available, could be used to confirm CAPRISA 004.[78] The trial was statistically powered to detect a relative risk reduction of 25% or more.[79] Moves toward licensing tenofovir gel faced a serious setback in November 2011, however, when the tenofovir gel arm was closed for futility after an interim

[78] CONRAD. FDA and CONRAD Chart U.S. Regulatory Path for 1% Tenofovir Gel for HIV Prevention: Collaborative meeting held with key stakeholders. 2010. Available at: http://www.conrad.org/media/news/88_CONRAD%20FDA%20Meeting%20Release%2020%20Final.doc. [Accessed 6 March 2013].

[79] Protocol. Microbicides Trial Network. MTN-003 Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women (VOICE). Version 2. Available at: http://www.mtnstopshiv.org/sites/default/files/attachments/MTN-003_FINAL_Version_2.0_31DEC2010.pdf Accessed 5 March 2013

analysis.[80] The analysis showed that HIV incidence was 6.1 percent in the placebo gel group and 6 percent in the tenofovir gel. Given that the trial had reached 75% of its endpoints, it was not possible that in the remaining time for a statistically significant result to be reached. Thus, rather than confirming CAPRISA 004, VOICE cast doubt on the 004 findings. Significantly, VOICE used a different dosing schedule to CAPRISA 004 – daily gel use, rather than the coitally dependant regimen. It had been hypothesised that this might enhance adherence, but the futility result suggests the opposite.

Subsequently the other two active arms in VOICE: oral tenofovir as PrEP and combined oral tenofovir/emtricitabine as PrEP, were also found to be ineffective in that trial.[81] Adherence to all interventions in VOICE was found to be very low, with on average less than 30% of women randomised to each of the interventions arms having detectable blood levels of the respective drugs (28% for oral tenofovir, 29% for tenofovir/emtricitabine and 22% for tenofovir gel).

The VOICE study does not show that the interventions are ineffective. The evidence shows that they were not effective *in the study population for that trial* due to adherence problems. VOICE provides a counterpoint to the CAPRISA 004 result that arguably justifies a further placebo-based trial, given the importance of having a more

[80] Microbicides Trials Network (MTN). MTN Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women. November 25, 2011. Available at: http://www.mtnstopshiv.org/node/3909 [Accessed 6 March 2013].

[81] J. Marrazzo, G Ramjee, G Nair, et al. *Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine or vaginal tenofovir gel in the VOICE study (MTN 003).* 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 26LB, 2013.

robust estimate of biological efficacy.[82] The importance of such a study being carefully designed to take into account the problem of poor adherence potentially confounding efficacy cannot be overestimated.

As tenofovir gel *was* effective in the CAPRISA 004 cohort, the reluctance of the regulatory agency to make the product available in a timely manner through an extension study is questionable, however. Firstly, women participating in this study were drawn from populations with very high HIV incidence. In addition, given the history of microbicide trials causing harms that only became apparent in efficacy studies, the women in CAPRISA were undertaking a significant risk, however well-minimised this was by the practices of the investigators. Sharing the benefits as well as the burdens of research is a fundamental tenet of research ethics and, given that adherence appears to have been a major factor in reducing the overall efficacy, open label access in which participants understand that they are taking a product that has offers partial efficacy is highly likely to have a positive impact of adherence behaviours. Further, the biological efficacy of tenofovir gel is supported by the step-wise relationship between better adherence and lower risk of HIV acquisition.

Had the CAPRISA extended access study, CARPRISA 008, commenced in 2010 rather than 2012, further information about the product efficacy in the cohort would have been available by the time that the VOICE interim analysis occurred. The prolonged gap before CAPRISA 008 began, and the limitations placed on the study population (the population who would thus obtain open-label access to tenofovir gel), shows how a conservative 'take' on efficacy data at a regulatory level can stymie investigator intentions to provide the kind of post-trial access recommended by the UNAIDS Ethical Guidance (2012). Guidance point 19 stipulates that once an HIV

[82] Indeed, the FACTS 001 study fills this function.

prevention intervention has been 'demonstrated to be safe and effective' it should be made available not just to trial participants but also to others at higher risk of HIV acquisition. The communities from which CAPRISA 004 participants were drawn had HIV incidences of 11% and 15% at the rural and urban sites respectively. In addition, former participants from HIV prevention trial that had not produced 'safe and effective' interventions were intended to be included – firstly, as their prior trial participation demonstrates that they have been assessed to be at high risk of HIV acquisition, and secondly as a gesture of reciprocity towards people who have contributed to clinical research. Of course the level efficacy of tenofovir gel is contested, and on that basis an argument can be made that limiting the trial population for CAPRISA 008 is protective – open label access to the gel might encourage risk taking, and the gel might provide inadequate protection. This position however seems unnecessarily paternalistic, and ignores the reality that many of these women may not be able to negotiate condom use, regardless of trial participation. In other words, the partially protective gel, with enhanced adherence measures, might be their best option.

Conclusion

Building on the findings of Heise et al.,[83] this study shows on the one hand that HIV prevention researchers recognise the importance of post-trial access to ARV for seroconverters, and have become increasingly adept at setting up the partnerships that facilitate this in instances where they do not directly provide ARV at trial sites. It also shows the complexity of post-trial access to successful products – 'post'-trial being

[83] L. Heise, K. Shapiro and K. West Slevin. 2008. Mapping the Standards of Care at Microbicide Clinical Trial Sites. Washington DC: Global Campaign for Microbicides.

something of a misnomer, given that the most timely and effective mechanism appears to be cross-over trial designs where participants on placebo arms are crossed over to active product, as in the instances of HPTN 052 and Partner PrEP. Extension studies commenced after trial results are released, as in the cases of TDF2 and CAPRISA 004, are sound in principle but in these instances were subject to delays beyond the control of investigators.

The delays experienced in setting up these extension studies point to a systemic issue in the translation of research results. If communities that participate in research are to benefit from its results, governments must be prepared to support the implementation of those interventions within their policy framework. This is easier said than done. In the instance of tenofovir gel, the modest efficacy combined with the conflicting data from VOICE created a dilemma for regulators which could not reasonably have been predicted. It seems unjust, though, that participants in the trial have to had to wait over two years to secure access, despite the great international acclaim with which this study was hailed,[84] due to issues regarding efficacy margins and breadth of the extension trial population. With regard to PrEP in Botswana, it is possible that a willingness to embrace ARV for prevention in HIV negative people has been affected by the stronger results of HPTN 052 showing the preventative efficacy of ARV when used earlier in positive people. While treatment-as-prevention does not provide the person at high risk of HIV acquisition with a new means of protection, it fulfils two functions simultaneously, and is easier to target than PrEP.

[84] AIDS 2010. 2010. Webcast: Safety and effectiveness of 1% Tenofovir Vaginal Microbicide Gel in South African Women: Results of of the CAPRISA 004 Trial. XVIII International AIDS Conference Vienna, ed. Available at: http://pag.aids2010.org/session.aspx?s=13#6 [Accessed 1 September 2013].

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Securing the reasonable availability of a successful intervention is intended to ensure that research conducted in lower income countries is responsive to needs, and does not exploit vulnerable population to test interventions for the consumption of those in high income countries. A major problem with this requirement, however, is the determining who is responsible for this form of access. It is clearly beyond the control of principal investigators, and is a matter for governments and their regulatory bodies – though sponsors certainly have a responsibility to actually apply for regulatory approval. The UNAIDS Guidance points to the engagement of 'national government, international organisations, development partners, representatives from wider affected communities, local authorities, international and regional non-governmental organizations, and the private sector' in addition to trial sponsors and researchers. Problems with post-trial access evidently occur when not all parties agree whether or not a new intervention should be made available for a given population at a particular time.

Careful alignment of national HIV strategies with approval criteria for ethical review committees might be a mechanism for ensuring that the research that goes ahead tests interventions that the national government will be prepared, later down the line, to fund, should the intervention prove successful. Even with such safeguards, however, political expediency may hamper funding, promotion and uptake of proven interventions – consider for example the Ugandan president's anti-circumcision statements,[85] and the tragically slow uptake of harm reduction for injecting drug users in the US.

[85] T. Kwidini. 2012. Uganda's president dismisses circumcision, HIV research. *Zimeye* 4 August 2012..

The inherent difficulties in achieving secure, ongoing access to effective interventions for trial participants and other communities at high risk of HIV acquisition does not mean it is unimportant. Rather, there is a need for further examination of when and how it works, and what factors are associated with failure so that procedural guidance can be refined and access maximised.

Part 3, Chapter 1

Ethics of ARV-based HIV prevention: Treatment-as-prevention and PrEP

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Abstract

Published data show that new HIV prevention strategies including treatment-as-prevention and pre-exposure prophylaxis (PrEP) using oral antiretroviral drugs (ARVs) are highly, but not completely, effective if regimens are taken as directed. Consequently, their implementation may challenge norms around HIV prevention. Specific concerns include the potential for ARV-based prevention to reframe responsibility, erode beneficial sexual norms and waste resources. This paper explores what rights claims uninfected people can make for access to ARVs for prevention, and whether moral claims justify the provision of ARV therapy to those who do not yet clinically require treatment as a way of reducing HIV transmission risk. An ethical analysis was conducted of the two strategies, PrEP and treatment-as-prevention, using a public health stewardship model developed by the Nuffield Council on Bioethics Council to consider and compare the application of PrEP and treatment-as-prevention strategies. We found that treating the person with HIV rather than the uninfected person offers advantages in settings where there are limited opportunities to access care. A treatment-as-prevention strategy that places all the emphasis upon the positive person's adherence however carries a disproportionate burden of responsibility. PrEP remains an important option for receptive partners who face increased biological vulnerability. We conclude that the use of ARV for prevention is ethically justified, despite imperfect global to drugs for those in clinical need. The determination of which ARV-based HIV prevention strategy is ethically preferable is complex and must take into account both public health and interpersonal considerations.

Introduction

Antiretroviral drugs (ARV) have been shown in several studies to be effective for HIV prevention, [1] using two quite different strategies. Treating people who have HIV with the specific goal of suppressing viral replication, and before they would normally need treatment for their own health, is known as 'treatment-as-prevention' (TasP) and reduces the risk of transmission to sexual partners by 96%[2]. Providing ARV to HIV negative people at high risk of acquiring HIV can occur either before the potential exposure as 'pre-exposure prophylaxis' (PrEP), which reduces the risk of becoming infected by 44[3]-75%[4] or after the exposure, as post-exposure prophylaxis (PEP).[5] This manuscript will only consider PrEP. The strategies differ, in that TasP puts the burden of HIV prevention onto the person with HIV, while PrEP puts it onto the HIV negative person, but they share many similarities. In both, the 'burden' comprises having medication prescribed, adhering to a dosing schedule, perhaps experiencing side effects, and having periodic medical tests.

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[1] S.S. Abdool Karim & Q. Abdool Karim. Antiretroviral Prophylaxis: a Defining Moment in HIV control. *Lancet* 2011; **378**(9809): e23-e25.

[2] M.S. Cohen, Y. Q. Chen, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New Engl J Med* 2011; **365**(6): 493-505.

[3] R.M. Grant, J. R. Lama, et al. (2010). Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *New Engl J Med* 2010; **363**(27): 2587-2599.

[4] J.M. Baeten, D. Donnell, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New Engl J Med* 2012; 367: 399-410..

[5] I.M. Poynten**,** F.Y. Jin, et al. Non-occupational post-exposure prophylaxis, subsequent risk behaviour and HIV incidence in a cohort of Australian homosexual men. AIDS 2009; **23***:*1119–1126.

Despite their recognised efficacy, there is debate about how these prevention strategies should be implemented in public health programs. Concerns include their impact on established prevention approaches such as condom use, the side effects of widespread additional use of potent drugs, the potential for coercive application of the strategies, and the diversion of ARV away from people with infection who need treatment for their own health.

Both HIV prevention and universal treatment access have been identified as global health priorities in the Millennium Development Goals[6], the WHO Political Declaration on AIDS in 2006 and the UN General Assembly of 2011. It is clearer than ever that they are complementary goals, in that reducing the number of new infections will decrease the need for treatment, and increasing the access to treatment will reduce the viral load in the population, and hence the risk of new infections. However, there is inevitably a tension between the two goals at a number of levels, most obviously in regard to resource allocation.

In this evolving context, we examined the perceived need for ARV-based prevention, in the form of PrEP and the moral claims that can be made for supplying ARV to people who are either HIV negative, or HIV positive but not at imminent risk of HIV-related immune damage. We considered whether or not, from a moral perspective,

[6] United Nations. 2008. The Millennium Development Goals Report. New York. Available at: http://www.un.org/millenniumgoals/pdf/The%20Millennium%20Development%20Goals%20Report%202008.pdf [Accessed July 30 2012.]

PrEP and TasP are strategies that meet important public health goals, and the extent to which they complement or compete with universal treatment access goals.

A public health stewardship framework

We chose to analyse both PrEP and TasP using a public health stewardship framework that seeks to balance individual autonomy with utilitarian and collectivist concepts of a common good. This approach is particularly suited for HIV prevention interventions, which involve the linkage of public health outcomes and human rights protections[7], thereby facilitating the active collaboration of people living with and affected by HIV. The Nuffield Bioethics Council proposes a stewardship model that asserts that acceptable goals for public health activities are:

- reducing the risks of ill health that result from other people's actions;
- reducing causes of ill health relating to environmental conditions;
- protecting and promoting the health of children and other vulnerable people;
- ensuring that it is easy for people to lead a healthy life;
- ensuring that people have appropriate access to medical services; and
- reducing unfair health inequalities.

These goals are considered to be acceptable, provided that they:

- do not attempt to coerce adults to lead healthy lives;
- minimise the use of measures that are implemented without consulting people (either individually or using democratic procedures);

[7] J. M .Mann. Medicine and Public Health, Ethics and Human Rights. *Hastings Cent Rep* 1997; **27**(3): 6-13.

- minimise measures that are very intrusive or conflict with important aspects of personal life, such as privacy.[8]

This framework is directly applicable to access to communicable disease control and specifically to HIV biomedical prevention interventions, as it articulates an approach to public health agenda, while recognising the need to minimise the impact on individual autonomy. In so doing it allows for a public health approach that fosters human rights protections because it recognises the importance of both individual and collective health, resisting the 'false dichotomy' between human rights and public health identified by Barr et al.[9]

Importantly, the framework recognises the ease with which an intervention facilitates 'a healthy life' as a significant public health goal. Past public discourses on HIV prevention have extolled the 'duty' to use a condom, or to adopt restrictive behavioural prevention practices, as if they were moral virtues in and of themselves.[10] In fact the long history of contraception has shown the difficulties that people experience in adhering to this kind of regime, rendering them potentially quite ineffective as public health strategies. The arrival fifty years ago of the contraceptive pill taught us that taking a pill to prevent potential unwanted consequences of sex is

[8] Nuffield Council on Bioethics. 2007. *Public health: ethical issues*. Chapter 2 (An Ethical Framework) Available at: http://www.nuffieldbioethics.org/sites/default/files/files/Public%20health%20Chapter%202%20-%20An%20ethical%20framework.pdf

[9] D. Barr, J. J. Amon, M. Clayton. Articulating A Rights-Based Approach to HIV Treatment and Prevention Interventions. *Current HIV Research* 2011; **9**(6): 396-404.

[10] M. Davis. The 'loss of community' and other problems for sexual citizenship in recent HIV prevention. *Sociology of Health & Illness* 2008; 30: 182-196.

far easier that using a barrier correctly and consistently for every penetrative sex act, and is consequently used, thereby yielding the public health benefit. Ease of use is integrally linked to the likelihood of effectiveness.[11]

As an HIV preventive intervention, PrEP reduces the risks of ill health that result from other people's actions - sexual partners who don't use barrier protection correctly or consistently[12] and 'environmental conditions', such as population HIV incidence that is so high that exposure is virtually inevitable. PrEP also protects the health of vulnerable people, in that people at increased risk of HIV are vulnerable in that respect if not in many other aspects of their lives. It is an 'appropriate medical service' in that it is an effective risk reduction tool, and reduces the inequality of some people facing disproportionate risk of HIV acquisition. Because of the adherence required, PrEP effectiveness is linked with voluntary, motivated and informed use in line with the principle of autonomy.

TasP also sits fairly comfortably in the stewardship framework. Like PrEP, TasP serves the public health goal of reducing risks of ill health resulting from other people's behaviour: People with HIV may experience pressure to disclose their HIV

[11] J.O. Kahn, J.N. Martin, M.E. Roland, J.D. Bamberger, M. Chesney, D. Chambers, K. Franses, T.J. Coates & M.H. Katz. Feasibility of Postexposure Prophylaxis (PEP) against Human Immunodeficiency Virus Infection after Sexual or Injection Drug Use Exposure: The San Francisco PEP Study. *Journal of Infectious Diseases* 2001; 183: 707-714.

[12] Where people have equal power, it is reasonable that they take equal responsibility for HIV/STI protection. However, condom use is not directly under the control of receptive sex partners, thus the receptive partner can be said to have less agency with regard to barrier protection.

status in situations where they feel it is unsafe to do so, such as negotiating condom use with a sexual partner, including a spouse; If they are effectively treated, the resulting viral suppression minimises the harm that can occur if positive people have unprotected sex. As TasP necessitates a focus on testing, more people knowing their HIV status and taking up the treatment option results in a lower 'community viral load', thus decreasing the overall environmental risk of HIV acquisition for others. It works to protect vulnerable people who fail to negotiate barrier protection and reduces the inequality of some people facing disproportionate risk of HIV acquisition by decreasing the risk itself, through reducing infectivity. Similarly to PrEP informed, motivated, voluntary uptake of TasP *is an exercise in autonomy*. However, lifelong adherence to medication is a huge commitment, particularly when started early. Unlike PrEP, the burden is unremitting once started, as taking breaks from treatment has been shown to lead to drug resistance and failure.[13] This aspect means it does not fit the criterion of making it easy to live a healthy life. The burden of treatment, however, is arguably offset by three factors: that some people with HIV prefer early treatment because it treats the 'illness' of being infectious, there is some preliminary evidence that suggests early treatment may be medically beneficial and that the point of diagnosis might be a critical juncture for linking in to treatment services, which in later HIV disease is crucial.

[13] J.D. Lundgren, A. Babiker, W. El-Sadr et al. Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4+ Cell counts and HIV RNA levels during follow-up. *J Inf Diseases* 2008; 197: 1145-1155.

PrEP

While the acquisition of HIV is preventable through the use of condoms and behavioural strategies such as celibacy or mutual monogamy, these strategies are of limited usefulness in many circumstances. Celibacy may be socially and/or economically impossible for many individuals. Mutual monogamy assumes that both partners are HIV negative from the outset, and that ongoing monogamy can be assured, whereas a body of evidence shows that this is unrealistic and many women worldwide have acquired HIV through their sole sexual partner[14]. Condom use requires the ability to both detect when there is a risk of HIV acquisition and negotiate condoms use for those acts, or use of condoms for all penetrative sex acts. While many commentators discuss the notion of 'responsible' sexual behaviour as a desirable moral norm, this overlooks the fact that HIV risk is largely determined by structural factors – the HIV prevalence in the demographic pool in which one has sex, rather than simply the sex one has, combined with the prevailing sexual mores. This is demonstrated by the fact that a woman from Kwa-Zulu Natal in South Africa faces a 25% lifetime risk of HIV acquisition, while an Australian woman's risk is less than a thousandth of that.[15] Given the difficulty of negotiating condom use in a variety of sexual scenarios and the dampening of sexual pleasure and/or erectile dysfunction that

[14] Jg Silverman et al. Intimate Partner Violence and HIV Infection Among Married Indian women. *JAMA* 2008 **300**(6): 703-710.

[15] B. Haire, J. Kaldor, C.J. Jordens. How Good Is "Good Enough?" The Case for Varying Standards of Evidence According to Need for New Interventions in HIV Prevention. *Am J Bioeth* 2012; **12**(6): 21-30. p 28

some experience when using condoms,[16] additional strategies to reduce HIV acquisition are desperately needed.

A particular appeal of PrEP is that it is the first regulator approved preventive intervention directly under the control of individuals at risk of HIV who have receptive vaginal or anal sex. The young women in southern Africa who are unable to insist upon condom use or faithfulness by their spouses, are equally unable to be able to prevail upon them to be tested for HIV, take up treatment, and ensure medication adherence to keep viral load suppressed, as would be required for TasP.[17] The moral imperative to enable the highest risk population in the world to protect themselves, requires a strategy that empowers them to be proactive on their own behalf, not one that positions them as hapless (or lucky) recipients of a fate determined by others' actions.

In summary, the moral argument for PrEP at an individual level rests on the need for preventive strategies in people facing an overwhelming risk. Existing tools are inadequate, particularly for the receptive sex partner who both faces a higher biological risk and has less control over the decision as to whether barrier protection is used. PrEP was developed for people in precisely this predicament. [18]

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[16] N.S. Musacchio, M. Hartrich & R. Garofalo. Erectile Dysfunction and Viagra Use: What's up with College-Age Males? *J Adolescent Health* 2006; 39: 452-454.

[17] S.S.Abdool Karim & Q. Abdool Karim. Antiretroviral prophylaxis for HIV prevention reaches a key milestone. *Lancet* 2011 (online first).

[18] PrEP may however also entail some social harms, as a person taking it may be presumed to be HIV positive and thus experience stigma. Thanks to an anonymous reviewer for this observation.

Treatment-as-prevention

Ongoing, secure access to ARV is critical for people with HIV, once a certain level of immune-system damage has been sustained.[19] TasP approaches have been criticised for prioritising a public health benefit – the suppression of viral replication, reducing infectivity – over the health of the patient, potentially leading to coercive regimes of testing and treatment without informed voluntary participation. [20]

These criticisms rest on several premises. The first is that there is a period after HIV infection but before significant immune damage in which it is valuable for the person with HIV to *not* commence treatment. In the absence of definitive evidence[21], this position is currently supported by several lines of reasoning. Specifically, it may be that starting ARV shortly after diagnosis extends the opportunity for poor adherence, for no clear benefit, which in turn can cause drug resistance, limiting treatment options later on. There is now clear evidence that interrupting treatment is associated with increased risk of disease progression and death[22]. Even the safest ARV

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[20] Strubb, S. 2012. Public Health or Slippery Slope? Poz Blogs, Poz. **2012**. Accessed July 31 2012

Strubb, S. 2010. Medical Ethics and the Rights of People With HIV Under Assault. Poz Blogs, Poz. 2012. Accessed July 31 2012

[21] It is not known whether there is a medical advantage is starting ARV very early in HIV infection. A randomised controlled trial, the START study, is evaluating this and results are expected within five years. http://www.niaid.nih.gov/volunteer/hivandinfectious/hivstudies/Pages/STARTStudy.aspx. Accessed July 31 2012

[22] The Strategies for Management of Antiretroviral Therapy Study Group. (2008). Major Clinical Outcomes in Antiretroviral Therapy (ART)–Naive Participants and in Those Not Receiving ART at Baseline in the SMART Study. *J Inf Diseases* 2008 **197**(8): 1133-1144.

regimens currently available can have serious short or long-term side effects, including altered lipids, reduced bone density and kidney damage.

Clearly, these are important individual considerations to be weighed against the potential public health benefit of having reduced infectivity. Their importance for an individual depends on contextual factors such as whether or not an individual is confident about taking medicine consistently, whether an uninterrupted supply is assured, and whether there will be a good opportunity to take up ARV at a later point if it delayed.

On the other hand, regardless of the medical implication of early treatment, suppressing viral load can also have the benefit of relieving the psychological burden that some people with HIV have expressed – the fear of potentially causing infection.[23]

The second premise is that it is morally wrong to situate the health of the person with HIV as secondary to the public health benefit of suppressing viral load, as occurs in a 'treatment-as prevention' strategy. At the individual level there is a clear responsibility for the physician to explain that early therapy may not be directly beneficial to the patient, and to present reasons why the patient may choose to decline early ARV. People may however prefer early treatment, for its impact on infectiousness or other reasons. If there is genuine voluntariness, the objection that the

[23] J. Gibbs. Verdict on a virus. IRMA Rectal Microbicides Advocacy blog. http://irma-rectalmicrobicides.blogspot.com.au/2011/11/pros-and-cons-of-treatment-as.html Accessed July 31 2012.

person with HIV is being coerced for societal benefit is neutralised. In addition, there is a sound rationale for offering early treatment: the risk of side effects is arguably mitigated by benefits in terms of reduction of inflammation, and the risks relating to non-adherence are under the patient's control to some extent). The public health goal is clear: reducing the risk of ill health that could come from the person with HIV having unprotected sex. Thus the benefit justifies the risk (which has been voluntarily assumed by the person with HIV), satisfying ethical criteria.[24]

Finally, there is the issue of coercion. Since the beginning of the HIV epidemic there have been periodic calls for coercive measures to isolate, control and in some cases criminalise people with HIV[25]. Coercive practices are unethical and specifically undermine effective HIV programs which ultimately rely upon people utilising services over lifetimes. Adherence to HIV treatment requires (at least) daily adherence to medication and this is only feasible when people voluntarily take on the responsibility.

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[24] Jaffe, H. W. and T. Hope (2010). "Treating for the Common Good: A Proposed Ethical Framework." *Public Health Ethics* **3**(3): 193-198.

[25] R. Bayer, R. 1989. Isolating the infected: the politics of control . *Private Acts, Social Consequences.* New York, The Free Press**:** 169-206.

Global Network of People Living with HIV. About the Global Criminalisation Scan. Available at: http://www.gnpplus.net/criminalisation. Accessed July 31, 2012.

International Planned Parenthood Federation, Global Network of People Living with HIV/AIDS, International Community of Women Living with HIV/AIDS. HIV - Verdict on a Virus: Public Health, Human Rights and Criminal Law. 2008. Available at: http://www.gnpplus.net/images/stories/2008_verdict_on_a_virus.pdf. Accessed July 31, 2012.

Rationing

A key concern is that expanding the criteria for treatment to include TasP for the newly diagnosed or PrEP for the HIV negative at high risk will reduce the availability of ARV for those who need it to maintain their health, meaning those who have symptomatic HIV disease or who are at imminent risk of disease progression.
It is not clear, however, that expanding the criteria for ARV will undermine access to ARV for those who need it for immediate health needs. As Barr et al point out, sustainable use of ARV for either treatment or prevention depends upon people seeking out services and in the case of treatment, using it for a lifetime.[26]Stigma, discrimination and lack of human rights protections jeopardise ARV programs because people become afraid of the social and political consequences of using them. Expanding the criteria for access has the potential to dilute association between ARV and negative social stereotypes (even so, there remains an imperative to address these issues both in terms of law reform for those subject to discriminatory laws and social empowerment of HIV-affected communities).[27]

In addition, many of the identified impediments to scaling up HIV treatment access are workforce and health system issues, including poor distribution systems, low remuneration for workers and accelerated migration of skilled workers[28]. Expanding

[26] Note 9, *op cit*

[27] *Ibid*

[28] Schneider, H., D. Blaauw, et al. (2006). Health Systems and Access to Antiretroviral Drugs for HIV in Southern Africa: Service Delivery and Human Resources Challenges. *Reproductive Health Matters* 2006; **14**(27): 12-23.

the criteria for ARV access, provided it occurs in a fashion that strengthens rather than undermines existing health infrastructure, has the potential to make efficiency gains across HIV programs.[29]

Mother-to-child prevention programs are a case in point.[30] Importantly, and despite the fact that women access ARV at higher rates than men in sub-Saharan Africa, mother-to-child prevention programs do not take treatment resources away from those in greater need – on the contrary, they have provided an important access point and facilitated the development of ARV services.

The public health goal in mother-to-child prevention programs is protecting and promoting the health of children. They are also grounded in a rights framework - the right to health. In the case Minister of Health vs Treatment Action Campaign[31], this right was upheld by the South African Constitutional Court, and the corresponding duty to provide the means to prevent the infection (ARV) was found to fall upon the South African Government. The responsibility of the government to intervene was because the risk was real – estimated as up to 30% without intervention – and effective risk mitigation was both available and feasible.

[29] G. Hirnschall, G. & B. Schwartländer. Treatment 2.0: catalysing the next phase of scale-up. *Lancet* 2012; **378**(9787): 209-211.

[30] There are a wide range of these programs, ranging from comprehensive programs that link the mother to ongoing care regardless of her CD4 cell count, to sub-optimal ones that provide singles doses of ARV to the mother and infant.

[31] http://www.saflii.org/za/cases/ZACC/2002/16.html

Importantly, mother-to-child prevention programs have been a mechanism for getting people into treatment programs. While such programs were initially used just to cover the pre- and immediate post- natal period, World Health Organisation guidelines now include an option for life-long access (known as the 'B+ option'), in recognition that cycling on and off ARV may be harmful to women's health, and that there are ongoing preventive benefits of continual treatment.[32]

The same argument now holds for population use of ARV-based prevention in adults, given evidence of efficacy and the high likelihood of HIV exposure for sexually active people in hyper-endemic settings, with the public health goal being the protection of vulnerable people. While population level treatment-as prevention is considerably more expensive that mother-to-child programs, prevention HIV now reduces pressure on ARV in the immediate future, thus arguably making ARV more sustainable for people who need it for their health. Without a significant decline in incidence, sustainability of treatment programs will be threatened as demand increases.

While governments can and must set spending priorities with regard to HIV treatment and prevention, supplying one group with ARV does not necessarily entail denying access to another group, if economies of scale are achieved. Clearly where the direct need of a person to be treated with HIV conflicts with the need of a negative person for PrEP, the health needs of the person with HIV must be addressed first because the

[32]World Health Organisation.April 2012. Programmatic Update: Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Executive summary. Available at: http://www.who.int/hiv/PMTCT_update.pdf [Accessed 20 November 2012]

life of that person depends on the supply of ARV, a need that trumps any potential prevention benefit. This does not imply, however, that the establishment of treatment-as-prevention and PrEP programs should wait until governments meet their commitments to existing universal access targets.

One of the fallacies in the 1990s debate over standards of care in research was that drug prices are immutable. The treatment access movement showed that drug prices do drop as a result of public pressure, and (some) pharmaceutical companies have shown themselves to be amenable to trade policies that facilitate access for those in low income countries, rather than adopting a protectionist stances. PEPFAR and the Global Fund have demonstrated that while providing ARV access is complex it can be progressively realised, and that successful programs breed successful programs. Rather than 'wasting' funds earmarked for HIV, widening the pool of those eligible for ARV by adopting 'treatment-as-prevention' may decrease the wastage that currently occurs wastage not just of resources, but more importantly of human life. Voluntary HIV testing is a cornerstone of HIV programs, but testing in itself is useless unless it links people to care. As Barr et al assert, testing is a tool, not a goal.[33] Current testing regimes linked to delayed ARV programs are not working optimally, according to a meta-analysis of 28 trials looking at people diagnosed with HIV but not yet eligible for ARV in sub-Saharan Africa. This study showed that more than two thirds of people tested positive were lost to care, meaning they never accessed treatment[34]. This is sobering. It suggests that diagnosing people with HIV, then telling

[33] Note 9 *op cit*

[34] S. Rosen & M. P. Fox. Retention in HIV Care between Testing and Treatment in Sub-Saharan Africa: A Systematic Review. *PLoS Med* 2011***; 8***(7): e1001056.

them to wait until their CD4 count drops, may not be a strategic use of resources in low and middle income countries. Diagnosing people with HIV and linking them to treatment, however, has twofold benefit: maintaining the health of the person with HIV, and protecting his or her sex partner/s[35].

Most-at-risk populations targeting

Age, gender and nationality, however, are not the only determinants of HIV risk. Both PrEP and TasP should be deployed to ensure access by those who most need them. This includes the most-at risk populations that exist within generalised epidemics, and care needs to be taken to ensure that the prevention programs do not further stigmatise these groups.

While the trial that established TasP was in serodiscordant couples, its mechanism of action is to reduce infectiousness to sex partners, so it should be available to on the basis of a positive person being sexually active with a partner or partners of unknown or negative status. It should be available to heterosexually and homosexually active people alike – trials of TasP in gay and MSM populations are infeasible post-HPTN 052, so the best that can be done is to extrapolate the findings, with the riser that as anal sex has a higher risk-per-act that vaginal, it might be somewhat less effective. Successful, cost-effective PrEP depends upon people who are at increased risk of HIV acquisition understanding this, seeking out PrEP, and adhering to the regimen for the period of time for which they are risk. This is complex, as even in sub-Saharan Africa there are heterogeneous risk factors in different regions.[36] Imposing eligibility

[35] Haire, B. (2011). Treatment-as-Prevention Needs to Be Considered in the Just Allocation of HIV Drugs. *Am J Bioeth* 2011; **11**(12): 48-50.

[36] http://transition.usaid.gov/our_work/global_health/aids/Countries/africa/hiv_summary_africa.pdf

constraints on PrEP in regions where HIV is hyper-endemic is problematic from a human rights perspective, however, due to the prevalence of violence and discrimination towards gay men and other men who have sex with men (MSM) in many African countries[37]. For PrEP to be meaningfully accessible to men at highest risk of HIV, those who have receptive anal intercourse with other men, an avenue for access without identifying as MSM is necessary. The recommendation for eligibility then would have to be for women and men who identify as being at high risk of HIV, without elaborate targeting that requires sexuality disclosure, as that could paradoxically exclude those at highest risk.

The situation for sex workers is complex, as their occupational health and safety is best protected by condoms.[38] Great care needs to be taken not to undermine condom culture in sex work, while still facilitating access to the full range of options for HIV prevention which workers might require for either professional or private sex practice. Involving sex workers in policy development around new HIV prevention technologies is critical to getting the balance right.

Targeting in concentrated epidemics

In developed countries with concentrated epidemics, PrEP is much easier to target, and is arguably the most effective way of utilising ARV for HIV prevention. In countries with universal health care systems and a clearly identifiable at risk population – the subsection of gay men and other MSM who have unprotected sex

[37]Note 9 *op cit*

[38] C.C. O'Connor, G. Berry, R. Rohrsheim & B. Donovan. Sexual health and use of condoms among local and international sex workers in Sydney. *Genitourinary Medicine* 1996; 72: 47-51.

with partners of unknown status – it is arguably more efficient to target these men to utilise PrEP than to attempt 'treatment-as prevention'. Recent Australian research has shown that men who identify themselves as being at high risk of HIV are willing to take PrEP, while those who perceive their risk as lower are less so[39]. The biological advantage of PrEP in a small epidemic is that it is more likely to provide protection in the highly infectious seroconversion period, when a person with newly acquired HIV has a high viral load but might not recognise that s/he has acquired HIV, and hence might not have yet accessed testing or treatment. That is not to say that treatment ought not to be available for people with HIV who perceive an advantage in early treatment, merely that in strategic terms, when the at-risk population is readily identifiable there are benefits both in terms of cost (the two drugs used in prevention being cheaper than three used in treatment) and in terms of providing protection on the basis of the negative person's risk practice rather than the positive person's apprehension of his need for treatment.

Conclusion

Both PrEP and treatment-as-prevention offer new ways to address HIV incidence. While ARV treatment is expensive, harnessing its preventative potential now will ultimately reduce demand on treatment resources. Treatment-as-prevention is more effective than PrEP, but its risks and benefits are likely to be weighed differently by individuals according to complex psychological rationale, and we consider that

[39] M. Holt et al. Willingness to use HIV pre-exposure prophylaxis and the likelihood of decreased condom use are both associated with unprotected anal intercourse and the perceived likelihood of becoming HIV-positive among Australian gay and bisexual men. *Sex Transm Infect*, 2012; 88, 258-263.

informed voluntary uptake is the only way for this option to be both ethical and effective. Wholesale uptake of treatment as prevention at the level required to make a major impact on the epidemic is therefore necessarily highly unlikely, at least until treatment regimens become more user-friendly or definite evidence emerges as to individual benefit of early treatment. PrEP offers a complementary modality than has the massive advantage of enabling people at risk to take control of their own protection, even if they are not so successful with condoms. This is a particularly welcome development for those who have receptive vaginal or anal sex.

In endemic or hyper-endemic settings, making both PrEP and treatment-as-prevention available, combined with human rights protection and empowerment of HIV-affected communities, makes more sense than trying to scale up testing and treatment alone. Adding PrEP into the toolbox for people who recognise that they are at high risk both supports the decline of HIV incidence while also changing the character of ARV access, disaggregating it from being a marker of HIV infection, which may assist in destigmatising it to some degree.

We recognise that there will be instances where rationing decisions need to be made as to whether an HIV negative person, a healthy HIV positive person or an HIV positive person with immune suppression will receive a limited supply of ARV. Where there is direct competition like this, we affirm the right to the sick person's need to be met above all other considerations. At the programmatic level, however, we argue that broadening the scope of ARV access to include both treatment as prevention and PrEP should occur now, and not wait until existing access targets are met, as the issue with ARV access is as much to do with infrastructure as it is with

supply, and new investment in ARV as treatment has the potential to increase efficiencies within the existing infrastructure, and complement the goal of universal access.

Part 3, Chapter 2

How good is 'good enough'? Determining when new HIV prevention technology should become standard of care.

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Abstract

In 2010, randomised controlled trials (RCTs) of two different biomedical strategies to prevent HIV infection had positive findings. However, despite ongoing very high levels of HIV infection in some countries and population groups, it has been made clear by regulatory authorities that the evidence remains insufficient to support either product being made available outside of research contexts in the developing world for at least two years. In addition, prevention trials in endemic areas will continue to test new interventions against placebo. But the judgments of evidentiary standards are never value-neutral. Using the recent trials and their contexts as case studies, we examine the basis for these decisions, which will potentially delay access to scientific innovation to the people who are most urgently in need of it.

Introduction

During 2010, in the space of five months, two landmark studies, CAPRISA 004 and iPrEX, showed convincing, positive results using related but different biomedical strategies to prevent HIV (Abdool Karim, Abdool Karim and Frolich et al.. 2010, Grant, Lama and Anderson et al.. 2010). Both studies found that their interventions had partial efficacy, meaning that they reduced, but did not eliminate the occurrence of new HIV infection. Both tested strategies involving antiretroviral drugs used in HIV negative people, but with different modes of administration – one a vaginally applied topical product, the other one orally administered. But neither product will be made available outside of the research in the developing world for at least two years[1]. In addition, neither product will be used as 'standard of prevention' in ongoing HIV prevention trials until confirmatory studies have been completed. In this article we examine the basis for these decisions, which will

[1] This is the estimated completion time of confirmatory studies. See Mail & Guardian 2011.

potentially delay access to scientific innovation to the people who are most urgently in need of it.

Reducing the incidence of HIV is both a public health priority and a moral imperative. Although World Health Organization (WHO) estimates of the extent of the international epidemic have declined slightly in recent years (UNAIDS 2010a), a number of southern African countries have estimated prevalence above 20% (UNAIDS 2010b) and current infection rates in the range of 1-5%. There are resurgent epidemics in gay men and men who have sex with men[2] in the developed world (van Griensven & de Lind van Wijngaarden, et al.. 2009), and despite the galvanizing of international will to provide universal access to antiretroviral drugs (ARV) over the last decade, the reality of treatment for all who need it remains a distant goal, particularly with the Global Financial Crisis having a potential impact upon key donors such as the President's Emergency Fund for AIDS (PEPFAR). Preventing HIV acquisition therefore, as well as treating those living with the virus, remains a critical public health goal in areas where HIV is endemic.

New biomedical products of moderate efficacy have the potential to significantly slow the epidemic in these affected countries. Delay in introducing effective prevention strategies may result in hundreds of thousands of potentially avoidable infections. It is therefore reasonable to ask on what basis was it decided a) that the two new trials do not provide sufficient evidence to support these products being made available outside research settings, and b) that they should not form part of the standard of care in the control arm of new trials, and replace placebos? The main sources of guidance available to make this judgement are specific ethical guidelines produced by UNAIDS/WHO (2007), the HIV Prevention Trials Network (2009) and UNAIDS/AVAC (2010), ethical analysis using the

[2] We distinguish 'gay' men from 'men who have sex with men' to acknowledge that homosexually active men have distinct and different social identities.

concept of equipoise, and regulatory requirements, in particular those of the US Food and Drug Administration (FDA).

Application of FDA guidelines immediately raises the question as to whether the level of evidence being required for US or other rich country settings is in the best interests of people at risk of HIV, and participants in new trials, in developing countries with a high incidence of HIV.

The recent trials

In July 2010 the ground-breaking results of the CAPRISA 004 trial were released to international acclaim (AIDS 2010), showing 39% efficacy of a vaginal microbicide using 1% tenofovir gel in a large scale IIB trial (Abdool Karim, Abdool Karim and Frolich et al.. 2010)[3].

In November 2010, the iPrEx results were published in the New England Journal of Medicine, showing a higher risk reduction than CAPRISA 004 (44%) using a combination of tenofovir and emtricitabine (TNF/FTC)[4] taken orally each day (Grant, Lama and Anderson et al. 2010).

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[3] Microbicides are topical agents, in this case in the form of a gel, containing the antiretroviral drug tenofovir. They are designed to prevent HIV acquisition when applied inside the vagina (products are also being developed for rectal use). In theory a microbicide product could empower women to protect themselves from HIV, as it could be used at a women's discretion and need not involve negotiation with a male sexual partner. In practice, development of products in this field has been beset with unexpected difficulties. The first product ever evaluated in an efficacy trial was associated with increased risk of HIV acquisition, closely followed by several other products with negative (though not necessarily harmful) results (Padian, Buvé and Balkus 2008).

[4] The product consisted of tenofovir – the same active ingredient in the CAPRISA 004 product, together with a second antiretroviral drug, emtricitabine, taken orally. The combination is available as a

While the effects of both these products appear modest compared to some preventive measures, such as infant vaccines, they are substantial in the context of HIV prevention, where there have been few technological advances, apart from male circumcision (which is a long-established practice used for a new purpose), in a quarter of a century[5]. Furthermore, the real benefit of these products might be substantially greater at the individual level, because the estimates found in the trials reflect the raw difference in HIV infection rates between the two randomised groups in each study, without regard to the extent to which participants actually used the study products.

As pill-taking and gel use are user-controlled activities that require on-going adherence, both studies had strategies for testing adherence so that the efficacy of the product in high adherers could be compared that in to low adherers. In the topical trial, adherence was tested using a biomarker on the applicator gel that reacted to vaginal fluid (applicators were returned to researchers). In the iPrEX trial, adherence was tested by measuring blood levels of the drug. For both studies, step-wise increases in efficacy were associated with evidence of adherence. In iPReX, high adherers were 73% less likely to acquire HIV than the placebo group (Grant, Lama and Anderson et al. 2010), and in CAPRISA 004, were 54% less likely

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single pill under the brand name Truvada, and is currently used in the treatment of people with HIV. The advantages of an oral product are again that it can be taken discreetly, but more importantly – like modern hormonal contraception – the act of protection is removed from the sexual context ('non coitally dependant', in medical parlance). This makes it something that can be integrated into daily routine, arguably facilitating adherence.

[5] Another biomedical strategy prevention strategy was found effective in May 2011. The study HPTN052 showed that early initiation of treatment in a person with HIV prevented HIV acquisition by that person's HIV uninfected sexual partner by 96%. Unlike PrEP and microbicide strategies, this approach works by reducing the infectivity of the index partner rather than directly blocking infection in the HIV negative partner.

to acquire HIV (Abdool Karim, Abdool Karim and Frolich et al. 2010). As adherence dropped, so too did efficacy in both studies. This strengthens the plausibility that reduction in HIV acquisition was due to the product, and suggests that the real efficacy of the products is very much higher than the estimate derived from the reported intent-to-treat analysis.

Adherence is critical to real world effectiveness of user-dependent methods. As Heise et al. (2010) point out:

> [W]ith user-dependent methods like microbicides or condoms, focusing on the method's efficacy alone misses half the story. The protection that a prevention method confers is a function of both the inherent efficacy of the method and how consistently it is used. Indeed, given the particular transmission dynamics of HIV, consistency directly compensates for efficacy. In other words, using a low-efficacy method consistently for HIV protection can confer as much protection as using a high-efficacy method inconsistently.

Taking a pill, for example, or using a gel that increases rather than dampens sexual pleasure (Stadler 2010) might prove to be more user-friendly than using a condom; and user-friendliness would promote adherence and thereby increase the real-world effectiveness of PrEP and microbicides in HIV prevention.

Ethical guidelines on standards of prevention and placebo

Three sets of guidelines provide specific advice on the standard of prevention issue in HIV prevention trials: UNAIDS/WHO in their ‘Ethical considerations in biomedical HIV prevention trials’ of 2007, HIV Prevention Trials Network (HPTN) in their Ethics Guidance for Research (2009) and UNAIDS/AVAC Good Participatory Practice Guidelines for HIV prevention trials (2010 consultation draft).

The 2007 UNAIDS/WHO guidelines replace an earlier document that was specific to HIV preventive vaccines, broadening the scope to the wider field of emerging HIV prevention technologies and encompassing social changes, such as the increased availability of antiretroviral therapy. It is in these guidelines, indeed, that the term 'standard of prevention' was coined, to distinguish it from its sibling, 'standard of care'. Guidance Point 13 on 'standard of prevention' and Guidance Point 15, on 'control groups' are particularly relevant here as they specify respectively what participants should receive in HIV prevention trials as standard care in general and in control groups.

Regarding the standard of prevention, Guidance Point 13 states:

> Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and *access to all state of the art HIV risk reduction methods* are provided to participants throughout the duration of the biomedical HIV prevention trial. New HIV risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities. (Guidance point 13, Standard of Prevention, our italics.)

UNAIDS /WHO guidelines make a normative statement – that researchers must ensure that participants in HIV biomedical prevention trials have access to all state of the art HIV risk reduction methods. It then goes onto make a procedural instruction, which is that researchers should negotiate the incorporation of new prevention methods into existing trials with research stakeholders, including the community. Negotiation, the guidelines state, should take into consideration feasibility, expected impact, and the ability to isolate the impact of the biomedical HIV modality being tested. Finally, the guidelines state that that new interventions should be added "as they are *scientifically validated*" (a concept that is left

undefined) or "as they are approved by relevant authorities". Scientific validation could be defined as evidence of efficacy as shown in a clinical trial, while "approval by relevant authorities" introduces an inevitable delay that depends on regulatory processes.

The normative statement in the UNAIDS Guidance Point 13 encapsulates a universalist stance in its directive to supply participants in HIV prevention trial with 'state-of-the-art' prevention interventions in the control arms of studies. The procedural point that follows, however, has the effect of opening up the standard for negotiation – a negotiation that is tipped in favour of research funders, particularly with respect to the provision regarding feasibility of subsequent trials, which is a determination that that can only be made by the research elite, and involves judgments of value as much as objective judgements.

So in effect, the UNAIDS Guidance Point 13 proposes a normative standard about how HIV prevention research is conducted,[6] however in the commentary the interests of both science and society are mentioned as factors that might provide reason *not* to supply 'state of the art' HIV prevention technologies, even before getting into what 'a proven intervention' means. Given that adding in new partially effective prevention interventions into trials testing other as yet unproven interventions will necessarily complicate research and require larger sample sizes and exponentially more funding, the commentary undercuts the norm.

Guidance Point 15, on control groups, provides somewhat clearer guidance. It defines the ethically acceptable use of a placebo control, limiting its use to situations where "there is no HIV prevention modality of the type being studied that has been scientifically validated in comparable populations or approved by relevant authorities." The accompanying commentary provides examples that recognise the limits to extrapolating assumptions about efficacy beyond the populations represented in available trial results. The wording however

[6]This follows from the principle that the interests of the research participant should take precedence over all other interests, in line with the Declaration of Helsinki (article 6).

still allows for the interpretation that a technology does not become standard of prevention until it has been 'approved by relevant authorities', an issue we will discuss further in the paper.

The HIV Prevention Trials Network (HPTN) Ethics Guidance for Research (2009) avoids the apparent contradictions in the UNAIDS/WHO by taking a pragmatic line, in which it parses the ethical aspect of standard of prevention into obligatory and aspirational elements. The full guidance point (9) states:

> In partnership with key stakeholders, HPTN should establish a package of effective, comprehensive and locally sustainable prevention services to be offered to participants in each HPTN study.

It then assigns 'provision of prevention package' to the status of 'ethical obligation' and 'content of prevention package' to the status of 'ethical aspiration'. Down-shifting the content of the package to 'aspirational' is a minimalist approach. It obviously gives researchers much greater leeway in designing studies, and indicates a shift away from a strict obligation-based framework. These guidelines introduce the concept that a prevention package provided in a trial should be 'locally sustainable', which both points toward an intertwining of research ethics and public health intervention (as discussed in Macklin 2010), along with a whiff of ethical relativism – that research participants are owed different duties according to where they live.

The other very specific set of guidelines is the UNAIDS/AVAC Good Participatory Practice Guidelines for HIV prevention trials. There is a 2010 iteration of these up for public comment that also uses the language of negotiation regarding the addition of newly validated HIV prevention technologies. Researchers are asked to 'review' prevention packages, and to 'negotiate' and 'consult'. The standard for what constitutes a proven intervention is vague,

and the wording shifts between ‘scientifically validated’ and the stricter ‘approv[al] by relevant authorities’.

None of the three sets of guidelines discussed here offers a clear normative standard for the content of the prevention package in HIV prevention research. The UNAIDS/WHO 2007 guidelines come closest, with their statement that participants should be offered ‘state-of-the-art’ prevention interventions.

Guidance based on the requirement of “state of the art” prevention for all trial participants

A central question posed by the both the CAPRISA 004 and iPrEx results is whether tenofovir gel and oral TNF/FTC must, as a result of their success in reducing HIV infection rates, now be considered ‘state-of-the-art’ HIV prevention, and thus be included in the control arms of subsequent prevention trials. In March 2009 USAID, in anticipation of such quandaries, the Global Campaign for Microbicides (GCM), UNAIDS and the Centers for Disease Control (CDC) met in Kampala, Uganda to discuss precisely how to determine when a prevention product should be deemed ‘state of the art’. They came up with a list of criteria that fall into four categories: the weight of evidence for a product and how this has been received by the broader scientific community; issues surrounding potential safety or cultural concerns; the feasibility of supplying the product; and the impact of adding the product to the enterprise of testing new HIV prevention modalities (McGrory et al. 2010).

Unlike male circumcision, the other new prevention technologies to emerge so far in HIV prevention – i.e. vaginal or rectal microbicides and oral prophylaxis - do not appear to present fundamental cultural issues for implementation, and both offer a form of protection that has hitherto been lacking in HIV prevention: a technology whose use is controlled by the receptive sexual partner. Regarding issues of safety, there are considerable safety data

available from earlier trials (e.g. Peterson et al. 2007). Feasibility of supplying a new product is always challenging, but in the end, a matter of distribution logistics. Thus the remaining issues are the weight of evidence and the impact of adding new technologies to the enterprise of HIV prevention research.

Large scale efficacy trials of new prevention technologies for HIV are generally powered to detect reductions in infection rates down to about 30%, the lowest level at which it is considered that an intervention would have an advantageous public health impact, based on mathematical modelling studies (WHO 2010). The absolute size of the impact in any particular region, however, depends upon the dynamics of the HIV epidemic in the region, its scale, and the extent to which other prevention interventions are being used.

Guidance based on drug development standards

Most drug development occurs in the developed world in an environment of intense commercial and academic competition. The United States' Food and Drug Administration handles high numbers of applications for the approval of new drugs, including applications for drugs that are very similar to drugs already on the market ('me too' drugs). In response, the FDA has developed stringent standards for evidence of efficacy (Hamburg 2010). One of the key elements of these standards is the requirement that the efficacy of a product be proven in two separate trials each of which must have a *p* value of less than 0.05 (Stone 2010, 25).

A *p* value of 0.05 is the accepted threshold of statistical significance. A *p* value is a measure of statistical significance, and a *p* value of 0.05 means that there is 1 in 20 probability that the results would have happened by chance if the factor being tested had in fact no effect – and the lower the number, the less likely that the result is due to chance.

Kopelman (1986) points out that while this is "a reasonable and well-established convention, it is none the less a moral choice" (Kopelman 1986, 322).

Alan Stone, writing on behalf of WHO, adds that in theory a single trial that is statistically significant at the 0.001 level rather than two trial with p values of 0.05 would suffice (alongside other non-RCT evidence). Indeed, an earlier breakthrough in HIV prevention – the mother-to-child transmission trial, known as PACTG076 that established the use of antiretrovirals to dramatically reduce transmission from mother to infant – became standard of care on the basis of a single trial, the *p* value for which was 0.00006 (Connor et al. 1994).

Stone identifies the requirement for two trials one after the other as potentially posing "insurmountable practical and ethical difficulties, particularly if the first trial showed evidence of protection with a *p* value well below 0.05." (Stone 2010, 25).The *p* value for the overall CAPRISA result was 0.017, with the 95 percent confidence interval[7] of 6 to 60%, placing this trial squarely in that realm identified by Stone as posing "insurmountable…difficulties".

The rationale for requiring confirmatory studies post CAPRISA is that the confidence intervals are wide. This is due in part to the fact that the trial was designed as a phase IIb study. Phase IIb studies have exponentially fewer participants that phase III efficacy studies, and these smaller sample sizes mean they are less likely to produce evidence of efficacy strong enough for regulatory approval. Essentially a phase IIb trial is an under-powered efficacy study designed to give preliminary evidence that a product works rather than an accurate estimate of its efficacy.

[7] A confidence interval is a range around an interval that conveys how precise and how stable a measurement is (New York Department of Health 1999). Wider confidence intervals indicate instability, meaning that if the trial were repeated the results could vary within that wide range

The iPrEx results are considerably stronger, with a *p* value of 0.005, and 95% confidence intervals of 32-74%. This means there is a 5 in 1000 probability that the result would have occurred by chance if the agent had no effect, and even the lowest end of the confidence interval is a level of efficacy that would, according to mathematical modelling, have significant public health benefits not only in regions where HIV is endemic (Anderson et al. 1996, Vermund 1998).

On October 25, 2010, The United States' Food and Drug Administration gave the go-ahead for fast tracking its review of tenofovir 1% vaginal gel, the product used in CAPRISA 004 (CONRAD 2010). This allows the product sponsors to submit each section of their New Drug Application for 'rolling review', a process which is more time-efficient, as some aspects of the application can be completed and submitted for review as further data are being gathered. Without a 'fast track' approval, the New Drug Application could not be submitted until all sections were complete, then the review would begin. The FDA stipulated the need for more data based on its preference for *two* well-controlled studies to verify the safety and efficacy of 1% tenofovir gel", so no final decision on licensure will be made until the results of another, confirmatory trial, which is due to end in 2013, are submitted (Global Campaign for Microbicides 2010).

In the case of oral tenofovir/FTC, although only one trial had been completed, the FDA requirement for two studies did not seem to be an impediment to the development of new prevention guidelines based on the findings of the trial. On January 28, 2011 the US Centers for Disease Control (CDC) released Interim Guidance: Pre-exposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men (CDC 2011) two months after the publication of the iPrEx results. This document provides a summary of the iPrEx results, with eligibility criteria and details of the medication regimen and recommended

follow-up, written in a way that suggested that it was aimed at healthcare providers and research-literate members of at-risk populations.

The interim Guidance follows an earlier CDC facts sheet, Pre-Exposure Prophylaxis (PrEP) for HIV Prevention: Promoting Safe and Effective Use in the United States which was released to coincide with the iPrEx publication. Despite the FDA's stated preference for two positive trials before licensing (Stone 2009), the CDC seemed to draw a more definitive conclusion, stating that "The iPrEx trial findings offer a new tool to help combat HIV among MSM, one of the hardest hit populations in the U.S. and many areas of the world" (CDC 2010).

The iPrEx product is a combination of the antiretroviral drugs tenofovir and emtricitabine (TNF/FTC), sold as the combination pill Truvada. The TNF/FTC combination pill is already in use for the treatment of HIV, so it could potentially be prescribed for the indication of prevention rather than treatment – particularly with the interim guidelines in place (unlike tenofovir gel for vaginal administration, which is not yet manufactured in commercial quantities). For gay men and men who have sex with men[8] in the US, access to this prevention technology is becoming a reality, although cost is currently a barrier.

In issuing guidelines for the use of TNF/FTC in HIV prevention the CDC, as a public health agency, has acknowledged that as the drug combination is already approved for HIV treatment, off-label prescription is a likely consequence of iPrEx, even before the regulatory body, the FDA, has considered licensing for that indication.

Despite recognition by the CDC that the TNF/FTC combination pill may now be used by MSM for HIV prevention purposes, it continues to be tested against a placebo comparator

in four out of five studies (AVAC 2010)[9]. The rationale for this is outlined by the US community advocacy organization AVAC (AIDS Vaccine Advocacy Coalition).

> These [iPrEx] data can't be extrapolated to people at risk of HIV via heterosexual sex or injection drug use. Differences in biology of the vagina and rectum, and between HIV risk in sexual versus injection exposure make it essential that ongoing placebo-controlled trials looking at PrEP in these contexts must continue.

There will inevitably be an element of judgement involved in deciding whether evidence in one setting (protection against rectal HIV exposure in men) can be translated into another (vaginal exposure in women)[10].

The somewhat unexpected results of a recent HIV prevention trial, FEM-PrEP, show there may be a valid scientific rationale for testing HIV prevention technologies according to exposure routes (rectal, vaginal, penile, injection-associated) rather than extrapolating results from one exposure route to another. FEM-PrEP was a placebo-controlled trial looking at the same PrEP drug as iPrEX – TNF/FTC in women at higher risk of HIV in three African countries. It closed prematurely in April 2011 when a scheduled analysis by the independent Data Safety and Monitoring Board ruled that the trial as designed would be highly unlikely to answer the scientific question of whether the intervention prevented HIV in women. The trial had reached 56 endpoints (HIV seroconversions) which were divided even between the placebo and intervention groups. Accordingly, the trial was stopped due to futility. At this

[9] The fifth study is a direct 'follow-on' study for iPrEx participants, which offers open label access to the drug for all, and provides less intensive counselling in order to get a more 'real world' result (AVAC 2010).

[10] While the premature closure of FEM-PrEP might suggest that there is a biological difference in the way that PrEP works in the setting of vaginal exposure, this presumption is premature until detailed information about drug adherence by FEM-PrEP participants becomes available.

stage it is unknown whether this unanticipated result was due to a biological difference (inadequate drug levels reaching the vagina) or some other factor, such as adherence (AVAC 2011).

Whether or not oral TNF/FTC is less effective, or ineffective, in women, there is now a range of prevention technologies for which there is RCT evidence that cover key sexual exposure routes: vaginal (tenofovir gel), penile (male circumcision and plausibly PrEP) and rectal (oral PrEP) – with two of these interventions evidenced by the result of a single trial.

The question that needs to be addressed is whether there is any latitude for allowing different standards of evidence to come into play, depending on the urgency and magnitude of the public health problem being addressed[11].

It is entirely reasonable to ask this question, given that drug regulation is reactive, and its systems change. A brief history of the FDA shows that until 1962, drugs only had to show safety, not efficacy, before licensing. Later, in response to thalidomide, regulators became so risk-averse that women of childbearing age were banned from participating in early-stage clinical trials altogether. As Edgar and Rothman note (1990), the post-thalidomide FDA adopted an adversarial rigour not only in the level of safety data required, but also in their aversion to the Type1 error (a statistical blip that produces false positive result in a clinical trial, when the result was due to chance). This perspective, which led to the requirement that efficacy be proven to a very high degree of stringency, was then changed by the persuasion of AIDS activists, who asserted that access to emerging therapies – use of 'any and all' therapies – was justified in a deadly epidemic, even if the approval system let through some drugs that were not truly effective (Edgar and Rothman 1990).

[11] Recall that from 1977 to 1993, women were not allowed in early stage FDA trials due to perceived risk, and data was routinely extrapolated from men.

This approach bore fruit. In 1987, pressure from AIDS advocates led the FDA to change its rules so that investigational drugs could be sold for serious or life-threatening diseases, well before they were proven to be effective according to the more demanding standards that had been previously in place (Edgar and Rothman 1990, 123). A year later, the FDA adopted a new regulation that involved the agency in the planning of research to assure a more efficient pathway through the regulatory system.

Current caution surrounding the new HIV prevention technologies stands in stark contrast to the arguments advanced by AIDS activists in the late 1980s.

The issues raised by new HIV prevention technologies are in some respects different to HIV treatment in the earlier years, in that there is already an effective prevention technology – the condom – and that effective treatments have become available so that infection is not a death sentence. Treatment, however, is expensive and inconvenient, has side effects, and may not be sustained in all contexts. Condoms require the willingness of the insertive partner to use one, and to use one correctly, in every instance in which exposure is possible. In southern Africa in particular there is an urgent need to break the cycle of infection through enabling receptive sex partners to control their own protection, thus microbicides and TNF/FTC offer a new avenue of risk reduction, and a chance to curtail the epidemic. It is also clear that for many people, the threat of infection remains as acute and irreducible as the threat of death was to people living with HIV in decades past.

Control groups in clinical trials

Turning to the impact of adding new technologies to the current standard of prevention, some participants in the Kampala Standard of Prevention consultation argued for a particularly stringent standard of accepted efficacy before a new prevention strategy would be classed as state-of-the-art and therefore required to be offered to all trial participants.

Applying the most stringent interpretation of the UNAIDS Guidelines (2007), they suggested that a new technology needed endorsement by normative agencies and approval by national regulatory authorities and even inclusion in national prevention policies where the trial is taking place (McGrory et al. 2010, 34). Each of these steps would involve at the very least several months, and more often several years, from the time of results being released to the point of licensure and inclusion in national strategic plans. The rationale for delaying the introduction of new prevention technologies in this manner rests on a utilitarian premise: that the development of maximally effective products justifies ongoing placebo-controlled trials. Delaying the introduction of partially effective technologies allows for simpler, faster and cheaper trials which maximise the opportunity for refinement of products and may expedite development of optimal prevention technologies. Better prevention technologies, the argument goes, would ultimately prevent more infections than addition on successive modestly effective interventions.

This approach offsets infections that could be prevented by the earlier introduction of modestly effective new technologies against infections prevented in the future using as yet unknown prevention technologies. This is a gamble, as there is no assurance that prevention technologies will increase in efficacy at a rate that justifies delay. It disturbs the deontological underpinnings of contemporary research ethics and posits a utilitarian approach – and one where the calculus rests upon the gamble that research is successful. This moral framework would be unlikely to gain support in industrialised countries, raising the question of why it would be considered in developing nations.

Setting the evidentiary bar high facilitates ongoing placebo-controlled trials, which makes research cheaper and more efficient. Faster research *might* result in finding more effective product more quickly. However there is no guarantee of this.

Universalism vs utilitarianism

The argument that research participants should be supplied with state-of-the-art prevention comes from a deontological (duty-based) perspective; it is grounded in the duty that a doctor has to act in the medical best interests of patients. This philosophical perspective deems clinical research to be akin to clinical practice, and underpins documents such as the Declaration of Helsinki. Denying a research participant access to best practice treatment or prevention for the purposes of a research study would be exploiting that person for the putative future benefit of others (in Kantian terms, treating the person as 'mere means'). This is a universalist perspective, which posits the duties owed to a person by merit of his or her personhood, as being the same as those owed to any other person, unless there are morally relevant differences. As Macklin (1999, 51) notes, universal principles 'require interpretation in the light of relevant empirical facts and contexts before they can be applied'.

A contrasting view is that those who participate in HIV prevention research studies usually reduce their risk of HIV acquisition and gain access to better medical services (in a tenofovir trial, for example, self-reported condom use rose from 52% to 95%, Peterson 2007). Furthermore, adding in newly validated prevention technologies would necessitate increased sample sizes and make it more difficult to get a clear answer to the research question. This perspective privileges the enterprise of HIV prevention research over the protection of individual trial participants, using the rationale that participants are already better off than the general local community. A problem with this perspective is that it takes a minimalist view of justice, apparently accepting the HIV incidence in southern Africa for example, as a given rather than an instance of injustice.

Clinical equipoise

The concept of equipoise provides another way to consider whether it remains acceptable to conduct placebo controlled trials when studies such as CAPRISA and iPReX have established the efficacy of specific prevention products. Equipoise posits that randomised controlled trials (RCTs) are morally justified where there is genuine uncertainly as to whether one therapy is superior to another (the received context is therapeutic rather than preventative). It is drawn from 'the principle of therapeutic beneficence and non-maleficence that apply in the traditional relationship between physician and patient' (Jansen 2005). Initially it was understood that the uncertainty needed to exist in the mind of the individual doctor (Fried 1974), but in 1987 a ground-breaking article by Freedman developed the concept that the 'genuine uncertainty' should be within the medical community, which he dubbed 'clinical equipoise'. Clinical equipoise – defined as an honest, professional disagreement among expert clinicians – is frequently cited as normative standard[12] of what remains a most contested concept (Ashcroft 1999).[13]

If the determination of equipoise depends on consensus within the medical community, vexed questions arise. How should we determine which members of the expert community must reach consensus? How many members should be involved? How can we be sure that a sufficient number or the "right" members have determined whether consensus does or does not exist[14]?

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[13] Of note, Freedman would take a dim view of the purposeful under-powering of IIb studies: "the results of a successful clinical trial should be convincing enough to resolve the dispute among clinicians" (1987, 144).

[14] The authors are grateful to an anonymous reviewer for raising this point.

Furthermore, the validity of *any* form of equipoise in clinical trials has been challenged (Miller and Joffe 2011; Miller and Brody 2003; 2007), with the argument that research is fundamentally different from medical treatment, as its goals are the production of generalisable knowledge, not the best interests of the patient/participant. Miller and Brody propose that non-exploitation of participants should be the norm that regulates research, not equipoise. However what they propose in its stead is a minimal sketch of an anti-exploitation norm which, taken to its logical conclusion, would require that research participants be either altruistic actors, or handsomely compensated, neither of which is reasonable or likely in HIV prevention research in the developing world (Schüklenk 2010, London and Zollman 2010).

So according to the Freedman model, neither CAPRISA 004 nor iPrEx disturbs clinical equipoise, because the medical and research community – which is made up of individuals who are directly invested in the ongoing project of HIV prevention research – has made this determination.

It is clear however that Freedman did not anticipate that a study with a *p* value of 0.017 – let alone one of 0.005 – would be deemed unconvincing, as he defines a successful clinical trial as one that disturbs equipoise.

In contrast to Freedman, Halpern (2006) offers a definition of equipoise that provides a seemingly objective standard:

> …that equipoise exists if well-designed studies have yet to answer the question as to which of the two interventions are to be preferred for a particular population of patients.

Halpern's definition is a neat, evidence-based solution that appears to avoid the consensus required by Freedman's notion of clinical equipoise. When applying it to the CAPRISA 004 and iPrEx results, however, it is clear that interpretation still has a role. For example, did CAPRISA 004 answer 'the question', or was it underpowered?

It is difficult to argue that iPrEx does not disturb equipoise, given that the level of evidence is deemed high enough for the CDC to issue interim guidelines for use (CDC 2011). The justification for ongoing placebo-controlled trials in this instance is that the trial population was limited to gay men and men who have sex with men. Adhering to literally to Halpern's 'particular population' specification in this instance means limiting potential access not only by gender but by sexual orientation, despite the facts that women are also exposed to HIV through receptive anal intercourse, and both heterosexually active and homosexually active men may be exposed through insertive sex. Indeed, if TNF/FTC provides a level of protection for a man exposed to HIV through unprotected anal sex, it is biologically plausible that it must also protect a man exposed through insertive vaginal sex. This raises issues of whether the limitations are politically, let alone scientifically, valid. Can results from a trial in gay men and men who have sex with men be extrapolated to men more generally (consider that in the post-thalidomide era of the 1970s and 1980s, extrapolation form men to women the standard practice)?

The apparent clarity of Halpern's equipoise quickly leads back into the same, value-laden territory.

Impact on future HIV research

Our key point about CAPRISA 004 and iPrEx is that different decisions could reasonably be made both regarding licensure and roll-out of the products in some areas where HIV is endemic, and in the composition of 'standard of prevention' in subsequent trials. For example, the South African regulators could have decided that, given South Africa's high HIV incidence in women, licensure of tenofovir gel was justified (presumably with some follow-on open label studies to gather more data). If the 39% efficacy rate of CAPRISA 004 translated into real-world effectiveness, this could have prevented 100,000 new infections per

year. While it could be argued that any modelling should be based on the lower end of the confidence interval, 6%, the higher level of efficacy shown in the more adherent trial participants is suggestive of higher, rather than lower, efficacy.

As we have explained in our discussion of the ethical guidelines, licensure of tenofovir gel in any country would have the flow-on consequence of requiring that tenofovir gel would need to be added into various other prevention studies as part of the 'standard prevention package'.

Standard of prevention and standard of care – new terms, old debate

In many respects, the issues raised in HIV prevention trial design as new technologies emerge are not new. 'Standard of prevention' is a new term for one aspect of the 'standard of care' debate that erupted in the 1990s. Briefly, 'standard of care' came to international attention in 1997 when placebo controlled trials of strategies for preventing mother-to-child HIV transmission in the developing world were criticised (Angell 1997; Lurie and Wolfe 1997). A partially effective intervention that substantially reduced transmission rates had been established by the PACTG 076 trial in 1994, but trials conducted in the developing world continued to be designed with placebo-controls. Using a placebo rather than an active control was inconsistent with the Declaration of Helsinki on this issue, and arguably exposed women and their foetuses to avoidable harm (e.g. Lurie & Wolfe 1997). Proponents of the trials responded that when research was designed to be responsive to the health needs of a particular setting, use of a placebo was justified if that was the operational standard available in that setting (e.g.Varmus & Satcher 1997). As Macklin (2001) notes, the issue was never resolved, and there are reasonable, well-informed people on both sides of the argument.

At the heart of the issue is a conflict between the obligation of a researcher to have a physician-like duty-of-care to research participants, and the need to research interventions that are applicable to health problems in the circumstances of the developing world.

This is salient to HIV prevention research, as introducing a newly validated intervention (tenofovir gel, TNF/FTC, or both) as 'standard of prevention' would require larger sample sizes and exponentially more funding and infrastructure for ongoing and planned trials. If the first successful technology is only modestly effective, its introduction as the new standard of prevention might effectively inhibit the search for optimal much more effective, affordable and sustainable HIV prevention technology. On the other hand, the populations enrolled in HIV prevention trials are among those at highest risk of acquiring HIV and it is not reasonable to withhold newly validated prevention technologies. The questions common to both the debate from the 1990s and the current issues in HIV prevention research are:

Are people exploited if they are exposed to sub-optimal treatment for the benefit of others? Should research participants have access to interventions that are significantly better than what is generally available in their countries? Are sub-optimal arms in research studies ethical if the research is intended to answer a significant question in global health?

Unequal negotiation

Current ethical guidance in HIV prevention trials places disproportionate emphasis on negotiation, which given the substantial inequities between the negotiating parties is likely to result in outcomes that suit the interests of research enterprise over the interests of the research participant. The rise of 'proceduralism' in ethics where processes of negotiation are privileged over setting normative standards, has been likened to "research at the auction

block" (London and Zollman 2010). The problem with auctions is that they enshrine the values of the market, not standards of fairness (Schüklenk 2010).

An important contextual issue to address here is that the issue at stake is standards of prevention, rather than treatment for an illness, and whether this makes a difference to the putative obligations to participants. Two fallacious points are frequently made regarding participants in HIV prevention research – the first is that if people 'engage in risky behaviour' (e.g. Bloom 1998, Slack et al. 2005), that puts them at risk of HIV acquisition, this cannot be said to create an obligation for researchers. The second is that even the standard prevention package in HIV prevention trials – a combination of counselling, condom provision and treatment for sexually transmissible infections – sets the bar too high for research, as these interventions are not representative of the prevention options available outside trials and are not sustainable after their conclusion (Padian et al. 2008 p 593).

The problem with the first point is that it assumes a disproportionate level of personal responsibility for what is essentially a structural risk – a woman in Kwa Zulu Natal in South Africa, for example, faces a 25% lifetime risk of HIV acquisition, while an Australian woman's risk is less than one thousandth of that (Camlin et al. 2010). Discourses of personal responsibility make no sense in the face of such odds, without even needing to go into issues of forced sex and sex as an economic imperative.

The problem with the second claim is that the emphasis on local standards outside the trial and sustainability of interventions beyond trial completion ignore the fact that the research context is different from the outside world. A duty of care is owed to research participants, hence 'standard of prevention' is pegged at international standards, rather than accepting the level of HIV risk and (lack of) access to risk-reduction in a trial community as an appropriate normative standard.

Conclusion

Both the iPrEX and CAPRISA 004 resist black-and-white determinations as to whether or not they should be implemented either programmatically or as standard of prevention. The problem with iPrEx is that the trial was limited by both gender and sexual behaviour. The problem with CAPRISA 004 is that the lower end of the confidence interval for tenofovir gel – 6% efficacy – would not constitute a useful or cost-effective intervention. But waiting for the results of trials that will not be completed for several years can be viewed as an inadequate response to these very promising data, given the urgency of need in southern Africa for new risk reduction interventions, and in particular those that are controlled by women.

As our discussion of the iPrEx and CAPRISA004 trials shows, evidentiary requirements and regulatory regimes are not objective standards, but involve moral decisions. Whether it is more important to eliminate any possibility of a Type 1 error, or to facilitate access to modestly effective, but imperfect, new technologies, is a question of values.

The competing interests are particularly difficult to navigate. On one hand, the enterprise of HIV biomedical prevention research – which holds out the hope of cheap, effective, user-friendly products – might be threatened if the new technologies become 'standard of prevention'. Proving a new intervention against the background of these partially effective technologies would require an exponential increase in sample sizes and budgets, threatening feasibility. People at high risk of HIV who enter prevention trials generally reduce their risk as a result of their participation (e.g. Peterson 2007), and arguably, this discharges the obligation to protect participants. On the other hand is there is the (contested) tenet from the Declaration of Helsinki that the researcher's *primary obligation* is to reduce risk for research participants, ahead of considerations of future beneficiaries of research. This is the basis upon which 'standard of prevention' packages are supplied – to

prevent the vulnerability of high risk populations being exploited for the future benefit of others, and to position the well-being of the research participant at the centre of the research endeavour.

Current guidelines do not solve the dilemma, because while UNAIDS stipulates use of “state of the art’ interventions in the control arm of HIV prevention trials, the definition of this term is vague until the point that regulatory approval is granted, which delays any obligation to provide a new technology potentially for years. The guidelines other than UNAIDS are weaker still, with prevention packages being undefined, and negotiation and consultation being emphasised over normative standards.

If the concept of equipoise is applied to the issues, the question then becomes, is there sufficient uncertainty regarding the results of CAPRISA 004 or iPrEx to continue with placebo-controlled trials? We have argued that there is no easy answer to this, as received models of equipoise are inadequate umpires. The strength of the evidence from RCTs must ultimately be evaluated, and this again requires value judgments.

Thus far, judgments have favoured the continuation of trials using placebo controls rather than the addition of one of both of the new technologies into the ‘standard of prevention’. This sits uncomfortably with the fact that the CDC is releasing interim guidance documents on TNF/FTC for US gay men and men who have sex with men (CDC 2011).

The decision to continue using placebo controls while waiting for the results of confirmatory studies of CAPRISA 004 and iPrEx means that a high incidence of HIV is maintained in populations in the developing world for efficient testing of other new prevention technologies in future trials. This is a significant moral choice that weighs the potential benefit of delay over the benefits of immediate rollout in areas where HIV is endemic. The populations likely to gain from these decisions are those at lower risk of HIV who already have good access to condoms, for whom only a very highly effective product

would be advantageous. It might mean that we are more likely to find a highly effective HIV prevention technology faster — although this is a gamble). It certainly means that in the immediate future, infections will occur that could have been prevented by early uptake of new technologies.

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References

Abdool Karim Q., Abdool Karim S. S. , J. A. Frohlich, et al.. 2010. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* **329**: 1168-1174.

Anderson, R. M. and G. P. Garnett. 1996. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *Lancet* **348** (9033): 1010-1013.

Angell, M. 1997. The ethics of clinical research in the third world. *New England Journal of Medicine* **337**(12): 847-849.

Ashcroft, R. 1999. Equipoise, knowledge and ethics in clinical research and practice. *Bioethics* **13**(3-4): 314-326.

AVAC. 2010. Frequently Asked Questions about PrEP and the iPrEx Trial

AVAC, November 23, 2010: p 6-7. Accessed 28 January 2011. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/31348

AVAC. 2011. Frequently asked questions about FEM-PrEP. Accessed 11 May 2011. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/33632

Bloom. B R. 1998 The highest attainable standard: Ethical issues in AIDS vaccines. *Science* 279: 186-188.

Camlin, Carol S., Victoria Hosegood, Marie-Louise Newell, Nuala McGrath, Till Bärnighausen, and Rachel C. Snow. 2010. Gender, migration and HIV in rural KwaZulu-Natal, South Africa. *PLoS ONE* 5 (7):e

Centers for Disease Control. 1999. Case-Control Study of HIV seroconversion in health-care workers after percutaneous exposure to HIV infected blood-France, United Kingdom, and United States, January 1988-August 1994, *Morbidity and Mortality Weekly Report.* 44:929-33

Centers for Disease Control 2010. Pre-Exposure Prophylaxis (PrEP) for HIV Prevention: Promoting Safe and Effective Use in the United States. Press statement. November 23, 2010.
Available at: http://www.cdc.gov/nchhstp/newsroom/PrEPforHIVFactSheet.html
Accessed January 23, 2010.

Centers for Disease Control. 2011. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. *Morbidity and Mortality Weekly Report* **60**(03): 65-68.

CONRAD.2010. FDA and CONRAD Chart U.S. Regulatory Path for 1% Tenofovir Gel for HIV Prevention: FDA has granted Fast Track approval designation for 1% tenofovir gel.Press statement. 25 October, 2010. Available at: http://www.natap.org/2010/newsUpdates/110110_01.htm Accessed January 23, 2010.

Edgar, H and Rothman, D. 1990. New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process. *Milbank Quarterly* **68**, Suppl 1: 111-142.

Fried C. 1974. *Medical experimentation: personal integrity and social policy.* Amsterdam: North-Holland Publishing.

Freedman, B. (1987). Equipoise and the ethics of clinical research. *New England Journal of Medicine* **317**(3): 141-145.

Global Campaign for Microbicides. Statement on FDA Regulatory Pathway for 1% Tenofovir Available at: http://www.globalcampaign.org/clientfiles/CONRAD%20FDA%20TFV%20GCM%20Statement.doc. Accessed 1 December 2010.

Grant, R. M. 2010. Antiretroviral agents used by HIV-uninfected persons for prevention: Pre- and postexposure prophylaxis. *Clinical Infectious Diseases* **50**(Supplement 3): S96-S101

Grant, R. M., J. R. Lama, et al.. 2010. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine* **363**(27): 2587-2599.

Heise, L.L., C.Watts, A. Foss, et al.. 2011. Apples and oranges? Interpreting success in HIV prevention trials. *Contraception* **83** (1):10-15.

International Rectal Microbicide Advocates. 2010. *From Promise to Product: Advancing Rectal Microbicide Research and Advocacy*. Pittsburgh, IRMA.

Jansen, L. A. 2005. A closer look at the bad deal trial: Beyond clinical equipoise. *Hastings Center Report* **35**(5): 29-36.

Kopelman, L. 1986. Consent and randomised clinical trials: are there moral or design problems? *Journal of Medicine and Philosophy* **11**: 317-345.

London, A.,and Zollman, K. 2010. Research at the auction block: Problems for the fair benefits approach to international research.*The Hastings Center Report*, **40**(4): 34-45.

Macklin, R. 1999. *Against relativism: cultural diversity and the search for ethical universals in medicine*. New York, Oxford University Press.

Macklin, R. 2001. After Helsinki: Unresolved issues in international research. *Kennedy Institute of Ethics Journal* **11**(1): 17-36.

Macklin, R. 2004. *Double standards in medical research in developing countries.* Cambridge; New York.

Macklin, R. 2010. Intertwining biomedical research and public health in HIV microbicide research. *Public health Ethics* 3 (3):199-209.

McGrory E, P. S., Hankins C, Paxton L, Heise, L. 2010. *Standards of Prevention in HIV Prevention Trials: Consultation Report and Recommendations.* Washington DC, Global Campaign for Microbicides at PATH.

Mail & Guardian staff reporter. 2011. Trial of HIV-prevention gel enters final phase. *Mail & Guardian*, 14 June 2011. Available at: http://mg.co.za/article/2011-06-14-trial-of-hivprevention-gel-enters-final-leg [Accessed 2 September 2013]

Merkatz, R. S. White Junod. 1994. The historical background of changes in FDA policy on the study and evaluation of drugs in women. *Academic Medicine* **69**(9).

Miller, F. G. and H. Brody. 2003. A Critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *The Hastings Center Report* **33**(3): 19-28.

Miller, P. B., Weijer, C. 2007. Equipoise and the duty of care in clinical research: A philosophical response to our critics. *Journal of Medicine and Philosophy* **32**(2): 117-133.

New York Department of Health. 1999.Confidence intervals: statistics teaching tools. Available at: http://www.health.state.ny.us/diseases/chronic/confint.htm Accessed 26 April 2011.

Padian N.S., Buvé A., Balkus J., Serwadda D., Cates W. Jr. 2008. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. *The Lancet.* Aug 16;372(9638):585-99.

Peterson, L., D. Taylor, R. Roddy, G. Belai, P. Phillips, K. Nanda,. 2007. Tenofovir disoproxil fumarate for prevention of HIV infection in women: A Phase 2, double-blind, randomized, placebo-controlled trial. *PLOS Clin Trial* 2 (5):e27.

Rennie S, J. Sugarman and the HPTN Ethics Working Group. 2009. HIV PreventionTrials Network Ethics Guidance for Research, HIV Prevention Trials Network.

Schüklenk, U. 2010. Calling it a day on proceduralism in bioethics? *Bioethics* **24**(9): ii-ii.

Slack, C., M. Stobie, et al. 2005. Provision of HIV treatment in HIV preventive vaccine trials: a developing country perspective. *Social Science & Medicine* **60**(6): 1197-1208.

Stadler J., E. Saethre. 2010. Blockage and flow: intimate experiences of condoms and microbicides in a South African clinical trial. *Culture, Health & Sexuality: An International Journal for Research, Intervention and Care* **13**(1): 31-34.

Stone, A. 2009. *Regulatory Issues in Microbicide Development.* World Health Organisation.

UNAIDS 2010. *Global report: UNAIDS report on the global AIDS epidemic 2010*. Joint United Nations Programme on HIV/AIDS (UNAIDS)
Available at:
http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123_globalreport_en%5B1%5D.pdf Accessed Jan 23 2011.

UNAIDS/WHO (2007). Ethical considerations in biomedical HIV prevention trials [monograph on the Internet]. Joint United Nations Programme on HIV/AIDS (UNAIDS).

UNAIDS.2010a. *Good participatory practice guidelines for biomedical HIV prevention trials. Draft for public comment, Second edition,* Joint United Nations Programme on HIV/AIDS.

UNAIDS 2010b. *2010: a Global view of HIV infection*. Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at:
http://www.unaids.org/documents/20101123_2010_HIV_Prevalence_Map_em.pdf
Accessed January 23, 2011.

Van Damme, L., G. Ramjee, M. Alary et al.. 2002. Effectiveness of COL-1492, nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *The Lancet* **360:** 971 - 977.

Van Damme, L., R. Govinden, F.M.Mirembe, et al.. 2008. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *New England Journal of Medicine* **359:** 463 - 472.

van Griensven, F., J. W. de Lind van Wijngaarden, S. Baral, and A. Grulich. 2009. The global epidemic of HIV infection among men who have sex with men. *Current Opinion in HIV and AIDS* 4 (4):300-307.

Varmus, H. and D. Satcher.1997. Ethical Complexities of Conducting Research in Developing Countries. *New England Journal of Medicine* **337**(14): 1003-1005.

Vermund, S. H. 1998. Rationale for the testing and use of a partially effective HIV vaccine." *AIDS research and human retroviruses* Suppl **3:**S321-3.

World Medical Association. 1964, amended 2008. *Declaration of Helsinki*.

Part 3, Chapter 4

It’s time: The case for PrEP as an active comparator in HIV biomedical prevention trials

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Abstract

In July 2012, based on evidence from two major trials, the United States Food and Drug Administration approved the use of combined oral tenofovir/emtricitabine as pre-exposure prophylaxis (PrEP) for people at high risk of HIV acquisition. PrEP effectiveness is marred by poor adherence, however, even in trial populations, thus it is not a magic bullet for HIV prevention. It is, however, the most effective biomedical HIV prevention intervention available for people at high risk of HIV, particularly those who have receptive sex and lack the power to negotiate condom use. Accordingly, there are compelling reasons to compare future experimental HIV prevention interventions against PrEP. The interests both of trial participants and of science are served by using PrEP as comparator: not only would HIV incidence be reduced, but also the question of whether new interventions were superior to best proven interventions, in a given setting, would be answered comprehensively.

Introduction

2012 saw a new optimism about ending AIDS, with the concept of 'an AIDS-free generation' becoming a concrete, if aspirational, goal (Knox and Doucleff 2012). This optimism is born of accumulating evidence that biomedical prevention interventions offer new approaches to preventing HIV infection, and that antiretroviral drug regimens (ARV) that are less toxic and more convenient stretch the life expectancy of people living with HIV toward 'normal' (May et al 2012). Despite a global decline in the incidence of HIV, global demand for ARV will continue to grow, however: of the estimated 34 million people with HIV, only eight million of these are on ARV, while another seven million require immediate treatment to which they do not have access (UNAIDS 2012). Of the 19 million remaining, they too will require treatment within the next six to ten years. Thus the number of people living with HIV, and needing treatment, continues to rise. Preventing new infections, and thereby not increasing the demand for ARV, remains critical. Research into new biomedical HIV prevention approaches needs to continue to expand the available options for people at high risk of acquiring HIV. New research into HIV prevention however needs to strike a balance between the urgent global need for new interventions and protection of the interests of people who participate in this research. This inevitably raises the issue of standards of care in trial design.

In the last two years, two new ARV-based prevention strategies have been shown to be effective: pre-exposure prophylaxis (PrEP) and treatment-as-prevention. This makes it possible for wide-scale ARV-based prevention programs to complement behavioural, barrier and structural interventions (Baeten et al 2012; Grant et al 2010; Thigpen et al 2012; Cohen et al 2011). A third strategy, an ARV-based microbicide,

awaits results of a confirmatory trial (Abdool Karim et al 2010)[1]. In short, what is possible in HIV prevention has changed dramatically in a short period of time – but what does this mean for the conduct of future research studies? Recent research findings pose a series of significant ethical quandaries for the design of new HIV prevention trials, particularly those that fall under the heading of 'standard of care'. With a swathe of partially effective options now proven, what should be in the control arm in new trials? What should the standard prevention package be for all participants?

This article considers standard of care in HIV prevention trial in the light of the recent announcement that the United States Food and Drug Administration (FDA) has approved combined tenofovir/FTC as pre-exposure prophylaxis (PrEP) (FDA 2012).

The efficacy trials

The series of positive trial results for the use of antiretroviral drugs (ARV) for HIV prevention began in 2010, with CAPRISA 004. This trial looked at the efficacy of 1% tenofovir gel formulated as a topical agent for intravaginal application (a microbicide), with coitally dependant dosing (before and after sex). Tenofovir is an ARV drug also used in HIV treatment. The study showed 39% efficacy which increased stepwise in participants who used the gel as directed (Abdool Karim et al 2010). This approach awaits results of a confirmatory trial, as the trial was designed as a 'proof of concept' study and lacked the statistical power for regulatory approval. Only months later, results from iPrEX were published, showing that combination

[1] Tenofovir gel works at a biological level as a form of topical pre- and post-exposure prophylaxis, but as taking an oral tablet is distinct from inserting a vaginal gel, the gel form and the oral form are usually seen as separate strategies.

tenofovir/FTC in tablet form (PrEP) reduced HIV acquisition by 44% in a population of men who have sex with men (MSM) and transgender women who have sex with men at high risk of HIV. Again, efficacy increased stepwise with good adherence to the study product to more than 90% (Grant et al 2010; Anderson et al 2012). Further evidence regarding tenofovir/FTC as PrEP came in 2011 from two trials in heterosexual people in Africa. The Partners PrEP study showed a 75% reduction in HIV incidence in couples where one partner was HIV negative and the other positive (serodiscordant couples), with tenofovir-only PrEP showing a 67% reduction (Baeten et al 2012). Finally the TDF2 study, which tested combined TDF/FTC PrEP conducted in heterosexual men and women in Botswana, showed a 62% reduction in HIV acquisition (Thigpen et al 2012).

In addition, a study testing the efficacy of early[2] ARV treatment for the HIV positive partner in serodiscordant couples (a strategy known as 'treatment-as-prevention') reduced HIV acquisition be a striking 96% (Cohen et al 2012).

These successes in ARV-based prevention sit alongside three randomised controlled trials which have shown that male circumcision can reduce HIV acquisition in heterosexual men by around 50% (Auvert et al 2005, Bailey et al 2007, Gray et al 2007), and a single vaccine trial that showed a modest 26% reduction in HIV acquisition (Rerks-Ngarm et al 2009).

[2] ARV treatment is defined as 'early' when it is administered in people whose CD4 cell levels are above 350.

This block of evidence means that HIV prevention has now advanced well beyond behavioural and barrier modalities alone, and this has ethical implications for the design of future studies.

Alongside the positive efficacy results, however, both PrEP (tenofovir alone and tenofovir/FTC) and tenofovir gel did not protect participants in the Fem-PrEP or VOICE trials, due to poor adherence (Van Damme et al 2012, MTN 2013). This suggests that there is still work to be done to establish an optimal prevention strategy that will be acceptable and usable for women at high risk of HIV acquisition.

Standard of Care and study design

'Standard of care' means the level of care provided to participants in a clinical trial. In HIV prevention trials, it can be used to describe four different aspects of care. Firstly, there is the 'standard of prevention', which is the risk-reduction package provided to all participants in the trial.[3] Secondly, 'standard of care' may be used to refer to the care provided to participants randomised to the comparator arm of a trial (van der Graff and van Delden 2009). Thirdly, there is ancillary care – health care that is provided to trial participants that is indirectly associated with the research, such as contraception and reproductive health care, cervical cancer screening and treatment for illnesses that arise during trial participation (Richardson 2007; Belsky and Richardson 2004). Finally, there is access to ARV for trial participants who acquire HIV on the trial (Macklin 2006).

[3] This term was coined in 2007 in the UNAIDS Ethical Considerations document to end the confusion caused my multiple meanings of 'standard of care'.

Both the standard of prevention (the care provided to all participants) and the choice of a comparator arm (the standard of care against which an experimental intervention is measured), have profound impact on the design of HIV prevention studies. For reasons of efficiency and cost-effectiveness, HIV prevention studies are conducted in populations of high HIV incidence (and these populations are usually in specific geographic areas), because this allows an expeditious answer to the research question. The studies need to enrol sufficient numbers of people to provide a statistically significant result, calculated using the background HIV incidence. The introduction of a highly effective standard of prevention – such as treatment-as-prevention, which has been shown to reduce HIV acquisition by 96% – would require such exponential expansion of the sample size as to make a trial impracticable.[4] For this reason, and because it is hard to justify withholding such an effective intervention in a study setting, it is likely that HIV prevention research targeting the specific population of serodiscordant couples will cease, and the focus fall on others at high risk of HIV acquisition. This article will therefore focus on people at high risk of HIV acquisition who are not in long-standing serodiscordant sexual partnerships.

The guidelines

There are several guidance documents that are relevant to the standard of care issue in HIV prevention trials.

[4] It could be argued that given such an effective intervention, the time has come to stop testing new approaches and to fully fund the global roll-out of early treatment for all people with HIV. This approach does not satisfy the requirement for HIV negative people at high risk to be able to protect themselves, however, and research is likely to continue until this need has been met.

The Declaration of Helsinki is a general guide to research ethics produced by the World Medical Association (WMA 1964; as amended in 2008), an international non-profit association of voluntary national medical associations formed in 1947. The Declaration drew upon the 10 points articulated in the Nuremberg Code and tied them in with physicians' obligations under the Declaration of Geneva (1948). It has since been revised six times, most recently in 2008.

The Declaration states in clause 6 that 'In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests'. Clause 32 goes on to address standard of care specifically:

> *The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:*
>
> *The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or*
>
> *Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.*

Thus the Declaration of Helsinki adopts a universalist position that prescribes a best current standard for research participants in all cases where the risk is serious or irreversible, such as the risk of HIV acquisition.

The International Ethical Guidelines for Biomedical Research Involving Human Subjects adopts a more pragmatic position. These guidelines were developed by the Council for International Organizations of Medical Sciences (CIOMS) in 1993, and revised in 2002. They were intended to assist developing countries to define national policies on the ethics of biomedical research involving humans, to apply ethical standards in local circumstances, and to establish or improve ethical review mechanisms. The CIOMS guidelines offer extensive commentary on the issue of standards of care in general and whether or not an active comparator or a placebo control may be used. The actual guideline (#11) is strict about the use of placebo were an established intervention exists, but it does not insist on the active comparator being the 'best'. Rather, it has to show *some* efficacy, allowing for the use of lower standards – or more technologically appropriate interventions – in specific instances, rather than a universal best practice. Guideline 11 states:

> *As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or ''no treatment''*
>
> *Placebo may be used:*
>
> - *when there is no established effective intervention; when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;*

- *when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.*

The CIOMS guideline is less prescriptive than the Declaration of Helsinki's clause 32 in that 'an established effective intervention' may be a local standard whereas the 'best current proven intervention' calls for an optimal standard. The gap between the two becomes apparent when considering the HIV prevention context: in a prevention trial in heterosexual serodiscordant couples, for example, the CIOMS guidelines would permit condom-based prevention only, while the Declaration of Helsinki could be used to argue for condom-based prevention, plus PrEP for the negative partner, early treatment for the positive partner, and access to male circumcision for HIV-negative male partners.

In addition to these general research guidelines, there are two set of ethical guidelines that deal specifically with HIV prevention trials, the UNAIDS Ethical Considerations in HIV Biomedical Prevention trials (updated in 2012) and the HIV Prevention Trials Network Ethics Guidance for Research (2009). These documents are complementary in some respects but they differ in the way that they outline the obligations regarding standards of prevention and care.

Guidance point 13 of the UNAIDS document, on standards of prevention, stipulates that there is an obligation to provide:

> *…access to all state of the art HIV risk reduction methods … to participants throughout the duration of the biomedical HIV prevention trial. New HIV-risk-reduction methods should be added, based on consultation among all research*

stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.

Like the Declaration of Helsinki, the UNAIDS/WHO guidance takes a universalist perspective, prescribing state of the art prevention interventions as standard of prevention. Morally relevant criteria, including scientific validation, approval by normative bodies and the impact on research feasibility, may influence whether or not a new modality is considered standard of prevention.

In addition to addressing standard of prevention, it also stipulates standards for ancillary care, specifically reproductive health care, treatment for sexually transmissible infections (STIs) and programs to address domestic violence.

Guidance point 15 of the UNAIDS document, on the control arm, supports point 13 by reiterating that "participants in both the control arm and the intervention arm should receive all established effective HIV risk reduction measures". In other words, experimental new interventions should be layered on top of what is already known to work. The allowable exceptions mentioned include instances where there is a sound biological rational for considering that an intervention shown effective in one population cannot be generalised to another, such as a vaccine tested against a particular subtype, or a product tested vaginally that cannot be extrapolated to rectal use.

The HPTN Guidance takes a different approach these issues. To begin with, it distinguishes between an ethical obligation and an ethical aspiration. Guidance point 9 on the standard of prevention identifies the provision of an effective prevention

package for trial participants as obligatory. The *content* of that package, however, is undefined except insofar as there must be established evidence of efficacy and the prevention interventions must be practically achievable and reasonably accessible in the trial setting. Using this framework, in settings where particular risk reduction methods are deemed culturally inappropriate or illegal, they need not be offered so long as some other effective form of prevention is offered. Provision of voluntary medical male circumcision or needle exchange programs are not required under these guidelines even if trials enrol HIV negative uncircumcised men or injecting drug users, if these are not reasonably available in local communities[5].

The HPTN document also provides guidance on aspects of research not detailed in the UNAIDS document, including specifying processes of community engagement, building capacity and partnerships, and attention to ancillary care.[6] Importantly, a new category of people to whom researchers have obligations is introduced – the 'screened out'. These are people who volunteer to participate in prevention trials but are found ineligible for reasons such as pre-existing undiagnosed HIV infection.

In addition to these two sets of guidelines, there is a set of consensus points developed by a group of HIV prevention researchers and bioethicists in 2009 that require consideration, from the 'Standard of Prevention' consultation in Uganda (McGrory et al 2010). These consensus points articulate that a new intervention is considered 'state

[5] While in-depth discussion of these issues are beyond the scope of this paper, conducting a trial in an area where participants are denied access to a proven safe and effective intervention for social or political reasons is both inappropriate and exploitative.

[6] UNAIDS deals with community engagement processes in detail in a separate document co-authored by UNAIDS and AVAC, the Good Participatory Practice Guidelines, first published in 2007.

of the art' when it is approved by a relevant regulatory authority or included in normative guidelines. They also stipulated that there was a strategic set of trials using PrEP in different populations that should be allowed to continue without alteration, regardless of whether early results showed efficacy, in order to get maximum information about PrEP in different populations.

The UNAIDS and HPTN documents will be discussed in detail in this chapter.

Key differences

The HPTN document was developed specifically to meet the needs of a research network undertaking HIV prevention work. It defines itself as 'pragmatic' rather than idealistic in its approach, and sets out to address 'limitations, gaps and inconsistencies' perceived in existing guidelines. It is structured to address issues that arise sequentially from before the trial to its aftermath, and it identifies which stakeholders are responsible for implementing which guidance points as well as defining the strength of guidance as 'obligatory' or 'aspirational', as noted above. In addition, it specifies a limited conception of justice in its underpinning principles – 'social justice', defined as "the ethical concerns related to treating people equally, avoiding exploitation, and trying to reduce health disparities" (Rennie and Sugarman 2010). Defining and limiting justice in this way prioritises equality between trial participants and their local communities rather than aiming to reduce health disparities between trial participants in high income countries and those in low and middle income countries.

While the UNAIDS guidelines impose duties on researchers to adopt international best practice, the HPTN document allows a looser standard to be adopted. The rationale for this is threefold: 'state-of-the-art' risk reduction methods that are not available outside the trial could constitute undue inducement to participate; to prevent research practices that would compromise 'real world' significance of data; and to guard against people within a trial having access to a higher standard of prevention than those outside it; (Rennie and Sugarman 2010). The focus on current local capacity reframes the discourse about double standards, generally understood to mean disparities between high income countries and developing countries, to one that centres on the local research community.

This brings us to the crux of the difference between the two sets of guidelines. With the FDA now having approved PrEP for HIV prevention, under the UNAIDS guidelines there is a prima facie requirement to provision PrEP as standard of prevention, as PrEP clearly meets the definition of 'state-of-the-art', having been approved by a normative body. Were this to occur, it would require much larger, more expensive and highly complex trials for subsequent experimental interventions – but these trials could dramatically decrease HIV acquisition in the trial populations. An argument against a 'state-of the art' PrEP-containing prevention package is that it could create serious inequities between trial participants and their communities in which PrEP is not available, though this could be rebutted on the ground that such provision would be a capacity building-enabler of better services in communities. Sustainability of the intervention is also an issue.

Under the HPTN guidelines, no such change is required, as these guidelines define a minimum standard that is amenable to ongoing research studies using the currently established standard of prevention (i.e. condoms, behavioural counselling and treatment for sexually transmissible infections), despite the fact that in the communities that have high HIV incidence, the inadequacy of existing methods is arguably well established. There is a clear tension between the imperative to protect participants and the imperative to find a cheap, effective user-friendly HIV prevention technology. Who gains from such studies is an important consideration – people in high incidence populations in low and middle income countries, or those in high income countries?

The mother-to-child transmission controversy revisited

These questions revisit the debate from the late 1990s about alleged doubled standards in mother-to-child prevention trials. A major ethical controversy erupted in 1997, when an article in the *New England Journal of Medicine* called into question placebo-based trials for mother-to-child HIV prevention in Africa and Asia, despite a proven effective intervention being published in 1994.The critics pointed out that the placebo-controlled trials violated the Declaration of Helsinki. They alleged that an unacceptable double standard regarding research ethics was operating, reminiscent of the notorious Tuskegee trial (Angell 1997; Lurie and Wolf 1997). Defenders of the trials argued the ‘standard of care’ established in the 1994 was not feasible in developing countries, that the placebo-based trials addressed a significant public health issue in those countries, and that the question that needed to be answered was whether the experimental therapy was better than nothing, not whether it was as good as an unattainable standard (Varmus and Satcher 1997).

The controversy led to a redrafting of the Declaration of Helsinki, but in the end the revised version(s) maintained that new interventions for serious conditions should not be tested against placebo when established treatment exists. Regardless of this outcome, bioethicists and researchers remain polarised on this issue (Macklin 2001). With respect to HIV prevention, the debate has slumbered as provision of behavioural and barrier prevention has been accepted by researchers and communities alike, and until very recently circumcision was the only proven biomedical intervention, which has a very specific population (heterosexual men) and is subject to profound social and cultural mores (Macklin 2008). The advent of ARV-based prevention reignites the issues.

Practical aspects

Amidst philosophical disagreement about standards, a focus on consensus-building processes among stakeholders including communities and actual and potential trial participants has emerged as a means for getting broad agreement of how research should be conducted in particular settings (for example, Vallely et al 2007). In 2007 UNAIDS and AVAC developed Participatory Practice guidelines (revised in 2012) that detail expected engagement with communities and the setting up of mechanisms that give communities opportunities for input throughout the research.

This is a very significant move, catalysed by the premature closure of PrEP trials in the early 2000s that were perceived to have been insufficiently consultative with trial communities, and which were perceived to be not sufficiently responsive the participants' needs (Forbes and Mudaliar 2009; Haire 2011; McGrory et al 2009; Ukpong and Peterson 2009).

Direct two-way communication with communities and giving community stakeholders real power to influence aspects of the research is a very important development. Community members do not meet with international researchers on an equal basis, however: there are vast power differentials at play. Indeed, the relationship has been defined as one of structural inequality, such that the researcher has a fiduciary responsibility to the research participant (Miller and Weijer 2006). Accordingly, while community collaboration with HIV prevention research is essential for best practice, it is no substitute for clear standards.

Making the call

The evidence that treatment-as-prevention, circumcision and PrEP are effective in preventing HIV acquisition means that it is no longer ethically appropriate to design HIV prevention without securing access to these interventions. Each of these strategies has been approved by a regulatory authority or in a normative guideline (the WHO in the case of circumcision, the International Antiviral Society, USA panel in the case of treatment-as-prevention, and the FDA in the case of PrEP).

Despite the recent advances in biomedical prevention, however, the need to develop new interventions remains. Longer-acting products in particular are required to avoid the problem of suboptimal adherence. A balance therefore needs to be struck between prioritising the protection of trial participants and facilitating ongoing research into new HIV prevention technologies that might be cheaper, more effective and more feasible in low- and middle-income countries.

Several different solutions have been proposed for the design of future prevention trials. Firstly, PrEP could be added into the standard of prevention and made available to all trial participants, who would be randomised to receive the experimental intervention or placebo on top of this background. The advantage of this is that it would be highly likely to reduce HIV acquisition very significantly in the trial population. The problem is that it would require very large sample sizes to obtain a result, and it might be difficult to untangle the efficacy (or not) of the experimental intervention from PrEP efficacy (which would likely be affected by differential adherence, as in trials to date).

A variation on this approach would be to allow PrEP in standard of prevention packages only where it is available in the community – namely, the US and at PrEP demonstration sites[7] – and not in other trial sites. There are serious objections to this. If the trial were only conducted in sites where PrEP was available, the same problems with very large sample size and difficulty in discerning the impact of the experimental intervention would apply. If some sites had PrEP access and others did not, a stark double standard would be in evidence, with the majority of HIV seroconversions likely to occur in the non-PrEP sites.

Alternatively, new trials could seek volunteers from amongst those who opt not to take PrEP, who could thus be randomised to experimental intervention or placebo. If it were the active choice of the volunteers not to take PrEP, there could be no ethical

[7] At the time of writing, the only demonstration sites launched were in the US, with others planned in two or three cities in Brazil.

objection. There are two problems with this, however. Firstly, in order for the choice to opt out of PrEP to be free, these studies would need to take place in setting where PrEP is available, which is a major constraint. Secondly, available research suggests that people who recognise themselves to be at high risk of HIV acquisition tend to be amenable to taking PrEP (Wheelock et al 2013, Holt et al 2011). People who don't wish to take PrEP may therefore be at lower risk, which would then require larger sample sizes to get a result, with the risk of a futile result.

Finally, there is the option of using PrEP as the active comparator. Again, there are several issues here. For this to be ethical, there would need to be strong preliminary evidence to suggest that the experimental intervention would be of comparative efficacy, so as to ensure equipoise (i.e. uncertainty as to whether one arm would be better than the other) between the two arms of the trial. The scientific objection to using PrEP as a comparator is the lack of precision regarding the preventative efficacy of TDF/FTC, with point estimates from randomised control trials ranging from 6% (FEM-PrEP) to 75% (Partners PrEP). An active comparator is usually required to have a substantial magnitude of effect, precisely estimated, with that estimate relevant to the trial population (Fleming 2013). This is not an insurmountable barrier, however. Further analyses of high adherers from iPrEx have shown efficacy of around 90% (Anderson et al 2012). Regrettably, similar information is not yet available regarding high adherence in women. Further, the requirement for a 'precise estimate' is questionable in this context, given that it has been well established that PrEP reduces HIV acquisition significantly when it is taken, but its effectiveness is attenuated by poor adherence (Mayer 2013). A long-acting intervention that had lower biological efficacy might work better than PrEP in one population and worse in another, more adherent one. Head-to-head studies are an opportunity to discover this.

Active comparator studies using PrEP also offer an opportunity to study further factors that relate to adherence in specific populations, and potential strategies for improvement.

PrEP is the appropriate comparator because there is good evidence that it works if people adhere to it. Adherence is a significant issue (Van Damme et al 2012; Beaten et al 2012), however, as is cost. It is not ideal, but in combination with existing barrier methods it is the best technology available for HIV negative women or men who have receptive sex. Finding an intervention that works as well as PrEP without requiring daily adherence would be a breakthrough. If a new experimental intervention failed to be as good as PrEP, then the trial would still be useful for getting further information about PrEP adherence in settings where HIV is hyper-endemic.

Voluntary circumcision for HIV negative heterosexual men should be offered as standard of prevention in studies that include this population, as it is feasible and cost-effective. Uptake of this option is likely to differ according to social and religious factors, but HIV negative heterosexual male participants in research studies should be allowed to make up their own minds, based on the evidence of safety and efficacy and their own personal values as to whether it is appropriate for them. The option should not be censored on the presumption of unilateral social and religious values in a community.

The recommendation to use PrEP as an active comparator arm, with circumcision offered as appropriate as standard of prevention, applies to trials that are in design phases. It would be counterproductive, for example, to try to add extra arms to trials

like FACTS 001, which is designed to meet the requirement of the South African regulatory authorities, and without which the question of how effective tenofovir gel is may never be answered comprehensively. Continuation of this trial should be supported for this reason. The continuance of PopART should also be supported, as this is a cluster trial testing an approach to the implementation of circumcision and treatment-as-prevention in a series of communities. PopART is not testing an experimental technology, but a particularly intensive approach to engaging people with proven HIV prevention practices, male circumcision and treatment-as-prevention.

Conclusion

In the absence of a universally acceptable, highly effective, cheap and user-friendly vaccine, HIV prevention research will continue to be an important component in the struggle to eliminate HIV. Despite its seemingly high biological efficacy, TDF/FTC PrEP is far from an ideal intervention, particularly given the serious problems with adherence shown in several of the trials to date. Even if adherence can be improved significantly in high-incidence populations through specialised programs, a short-acting user-dependent prevention technology is vulnerable to a range of potential disruptions. For people who are at high risk of HIV acquisition (from risk factors other than a serodiscordant regular sex partner), however, PrEP is the best adjunct to barrier and behavioural prevention that we have. Certainly there needs to be better data on how to use it optimally, but this can be gathered in studies that use PrEP as a comparator against which other experimental interventions are tested.

The goals of HIV prevention research must be to find the most effective ways of using existing tools, including PrEP, and to establish the effectiveness of new tools.

Randomised controlled trials are an important part of this, but they need to be designed in such a way as to ensure that all participants receive effective interventions, even though this necessarily means that trials will need larger sample sizes. HIV prevention trial participants are among the most vulnerable to HIV in the world, and need to be protected.

Incorporating TDF/FTC PrEP as the comparator arm in forthcoming HIV prevention trials balances the need for ongoing research with appropriate protection for research subjects. While a daily tablet is not an ideal prevention intervention, as it is vulnerable to stock-outs and to individual forgetfulness, it has the advantages of being separable from each sex act and appropriate for receptive sex partners. For HIV negative people at high risk of HIV acquisition, it is the best protection currently available. If we take seriously the moral imperative to address HIV incidence in those populations most vulnerable to HIV acquisition, then PrEP needs to be the comparator in forthcoming research.

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References

Angell, M. 1997. The ethics of clinical research in the third world. *New England Journal of Medicine* 337 (12):847-849.

Auvert, B., D. Taljaard, E. Lagarde, J. Sobngwi-Tambekou, R. Sitta, and A. Puren. 2005. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLoS Med* 2 (11):e298.

Bailey, R.C., S. Moses, C.B. Parker, et al. 2007. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *The Lancet* 369:643 - 656.

Abdool Karim Q., S. S. Abdool Karim, J. A. Frohlich,et al. 2010. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 329 (5996):1168-1174.

Baeten, J. M., D. Donnell, P. Ndase, et al. 2012. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine* 367 (5):399-410.

Belsky, L., and H. S. Richardson. 2004. Medical researchers' ancillary clinical care responsibilities. *British Medical Journal* 328 (7454):1494-1496.

Cohen, M. S., Y. Q. Chen, M. McCauley, et al. 2011. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine* 365 (6):493-505.

Fleming, T. 2013. Non-inferiority clinical trials. Some key consideration in PrEP and microbicide studies. Presentation at the meeting on the Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues, Washington, January 7 2013.

Available at: http://www.hivforum.org/storage/hivforum/documents/FutureofPrEP/session_2_fleming.pdf Accessed February 1, 2013.

Food and Drug Administration. (FDA). 2012. FDA Approves First Drug for Reducing the Risk of Sexually Acquired HIV Infection. (News release) July 16 2012. Silver Spring, MD: FDA. Available at:

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm (accessed September 10, 2012).

Forbes, A., S. Mudaliar. 2009. Preventing Prevention Trial Failures: A Case Study and Lessons Learned for Future Trials from the 2004 Tenofovir Trial in Cambodia Washington: Global Campaign for Microbicides.

Grant, R. M., J. R. Lama, P. L. Anderson, et al. 2010. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *New England Journal of Medicine* 363 (27):2587-2599.

Gray, R.H,. G. Kigozi, D. Serwadda, et al. 2007. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 369:657 - 666.

Haire, B. G. 2011. Because we can: Clashes of perspective over researcher obligation in the failed PrEP trials. *Developing World Bioethics* 11 (2):63-74.

Holt M., D.A. Murphy, D. Callander, et al. Willingness to use HIV pre-exposure prophylaxis and the likelihood of decreased condom use are both associated with unprotected anal intercourse and the perceived likelihood of becoming HIV positive among Australian gay and bisexual men. *Sexually Transmitted Infections*. 2012; 88:258–63.

Knox, R. and M. Doucleff. 2012. Clinton Reveals Blueprint For An 'AIDS-Free Generation'. *Shots: Health News*. http://www.npr.org/blogs/health/2012/11/29/166154269/clinton-reveals-blueprint-for-an-aids-free-generation.

Lurie, P., and S. M. Wolfe. 1997. Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries. *New England Journal of Medicine* 337 (12):853-856.

McGrory, E., A. Irvin, L. Heise. *Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site. Washington, DC: Global Campaign for Microbicides at PATH; 2009. Available at: www.globalcampaign.org/clientfiles/Cameroon.pdf (accessed: 8 January 2011).*

Macklin, R. 2001. After Helsinki: Unresolved Issues in International Research. *Kennedy Institute of Ethics Journal* 11 (1):17-36.

Macklin, R. 2006. Changing the Presumption: Providing ART to Vaccine Research Participants. *The American Journal of Bioethics* 6 (1):1 - 5.

Macklin, R. 2008. Standard of care: an evolution in ethical thinking. *The Lancet* 372 (9635): 284-285.

McCormack, S. Perspectives of a clinical researcher at the stage of grant writing. Standards of care in Future Microbicides Research Symposium. Presentation at the M2012 symposium. Microbicide 2012, Sydney, Australia. April 15th to 19th, 2012.

May M., M. Gompels & C. Sabin. 2012. *Life expectancy of HIV-1-positive individuals approaches normal, conditional on response to antiretroviral therapy: UK collaborative HIV cohort study.* Eleventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract O133, 2012.

Mayer, K. 2013. Future of PrEP and Microbicide Research: Setting the Stage. Presentation at the meeting on the Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues, Washington, January 7, 2013. Available at:

http://www.hivforum.org/storage/hivforum/documents/FutureofPrEP/session_1_mayer.pdf (accessed February 2, 2013).

Microbicide Trials Network. (MTN). 2013. Understanding the results of VOICE. Available at: http://www.mtnstopshiv.org/news/studies/mtn003 Accessed 12 March 2013.

Miller, P.B., and C. Weijer. 2006. Fiduciary Obligation in Clinical Research. *The Journal of Law, Medicine & Ethics* 34 (2):424-440.

Philpott, S., K. West Slevin, K. Shapiro and L. Heise. 2010. Impact of Donor-imposed Requirements and Restrictions on Standards of Prevention and Access to Care and Treatment in HIV Prevention Trials. *Public Health Ethics* 3 (3):220-228.

Philpott, S., L. Heise, E. McGrory, L. Paxton, C. Hankins, and the participants in the GCM/CDC/UNAIDS Consultation on Standards of Prevention in HIV Prevention Trials. 2011. The challenge of defining standards of prevention in HIV prevention trials. *Journal of Medical Ethics* 37 (4):244-248.

Rennie S., J. Sugarman and the HPTN Ethics Working Group. 2009. HIV Prevention Trials Network Ethics Guidance for Research. HIV Prevention Trials Network. Available at: http://www.hptn.org/web%20documents/EWG/HPTNEthicsGuidanceV10Jun2009.pdf (accessed July 31, 2012).

Rennie, S., and J. Sugarman. 2010. Developing ethics guidance for HIV prevention research: the HIV Prevention Trials Network approach. *Journal of Medical Ethics* 36 (12):810-815.

Rerks-Ngarm, S., P. Pitisuttithum, S. Nitayaphan, et al. 2009. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *New England Journal of Medicine* 361 (23):2209-2220.

Richardson, H. S. 2007. Gradations of Researchers' Obligation to Provide Ancillary Care for HIV/AIDS in Developing Countries. *American Journal of Public Health* 97 (11):1956-1961.

Thigpen, M. C., P. M. Kebaabetswe, L. A. Paxton, et al. 2012. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *New England Journal of Medicine* 367 (5):423-434.

Ukpong, M., and K. Peterson, eds. 2009. *Oral Tenofovir Controversy II: Voices from the Field*. Falomo, Nigeria: New HIV Vaccines and Microbicides Society (NHVMAS).

UNAIDS. 2011. Good participatory practice: Guidelines for biomedical HIV prevention trials 2011. 2nd ed. Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf (accessed February 2, 2013).

UNAIDS. 2012. *Global report: UNAIDS report on the global AIDS epidemic 2012*. Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at:

http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf (accessed January 30, 2013).

UNAIDS/WHO. 2012. Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS/WHO Guidance Document. (English original 2007, additional guidance point added 2012). Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO). Geneva: UNAIDS and World Health Organization. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf (accessed January 14, 2013).

Vallely, A., C. Shagi, S. Kasindi, et al. 2007. The benefits of participatory methodologies to develop effective community dialogue in the context of a microbicide trial feasibility study in Mwanza, Tanzania. *BMC Public Health* 7:133.

Van Damme, L., A. Corneli, K. Ahmed, et al. 2012. Preexposure Prophylaxis for HIV Infection among African Women. *New England Journal of Medicine* 367 (5):411-422.

van der Graaf, R., and J. J. M. van Delden. 2009. What is the Best Standard for the Standard of Care in Clinical Research? *The American Journal of Bioethics* 9 (3):35-43.

Varmus, H. and D. Satcher. 1997. Ethical Complexities of Conducting Research in Developing Countries. *New England Journal of Medicine* 337 (14):1003-1005.

Wheelock, A., A. B. Eisingerich, J. Ananworanich, et al. 2013. Are Thai MSM Willing to Take PrEP for HIV Prevention? An Analysis of Attitudes, Preferences and Acceptance. *PLoS ONE* 8 (1):e54288.

World Medical Association. 2008. *Declaration of Helsinki*, amended. Originally published 1964. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html Accessed February 6, 2013.

World Medical Association. 1948. *Declaration of Geneva*. Available at: http://en.wikipedia.org/wiki/Declaration_of_Geneva (accessed February 6, 2013).

Part 3, Chapter 4

It’s time: The case for PrEP as an active comparator in HIV biomedical prevention trials

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Abstract

In July 2012, based on evidence from two major trials, the United States Food and Drug Administration approved the use of combined oral tenofovir/emtricitabine as pre-exposure prophylaxis (PrEP) for people at high risk of HIV acquisition. PrEP effectiveness is marred by poor adherence, however, even in trial populations, thus it is not a magic bullet for HIV prevention. It is, however, the most effective biomedical HIV prevention intervention available for people at high risk of HIV, particularly those who have receptive sex and lack the power to negotiate condom use. Accordingly, there are compelling reasons to compare future experimental HIV prevention interventions against PrEP. The interests both of trial participants and of science are served by using PrEP as comparator: not only would HIV incidence be reduced, but also the question of whether new interventions were superior to best proven interventions, in a given setting, would be answered comprehensively.

Introduction

2012 saw a new optimism about ending AIDS, with the concept of 'an AIDS-free generation' becoming a concrete, if aspirational, goal (Knox and Doucleff 2012). This optimism is born of accumulating evidence that biomedical prevention interventions offer new approaches to preventing HIV infection, and that antiretroviral drug regimens (ARV) that are less toxic and more convenient stretch the life expectancy of people living with HIV toward 'normal' (May et al 2012). Despite a global decline in the incidence of HIV, global demand for ARV will continue to grow, however: of the estimated 34 million people with HIV, only eight million of these are on ARV, while another seven million require immediate treatment to which they do not have access (UNAIDS 2012). Of the 19 million remaining, they too will require treatment within the next six to ten years. Thus the number of people living with HIV, and needing treatment, continues to rise. Preventing new infections, and thereby not increasing the demand for ARV, remains critical. Research into new biomedical HIV prevention approaches needs to continue to expand the available options for people at high risk of acquiring HIV. New research into HIV prevention however needs to strike a balance between the urgent global need for new interventions and protection of the interests of people who participate in this research. This inevitably raises the issue of standards of care in trial design.

In the last two years, two new ARV-based prevention strategies have been shown to be effective: pre-exposure prophylaxis (PrEP) and treatment-as-prevention. This makes it possible for wide-scale ARV-based prevention programs to complement behavioural, barrier and structural interventions (Baeten et al 2012; Grant et al 2010; Thigpen et al 2012; Cohen et al 2011). A third strategy, an ARV-based microbicide,

awaits results of a confirmatory trial (Abdool Karim et al 2010)[1]. In short, what is possible in HIV prevention has changed dramatically in a short period of time – but what does this mean for the conduct of future research studies? Recent research findings pose a series of significant ethical quandaries for the design of new HIV prevention trials, particularly those that fall under the heading of 'standard of care'. With a swathe of partially effective options now proven, what should be in the control arm in new trials? What should the standard prevention package be for all participants?

This article considers standard of care in HIV prevention trial in the light of the recent announcement that the United States Food and Drug Administration (FDA) has approved combined tenofovir/FTC as pre-exposure prophylaxis (PrEP) (FDA 2012).

The efficacy trials

The series of positive trial results for the use of antiretroviral drugs (ARV) for HIV prevention began in 2010, with CAPRISA 004. This trial looked at the efficacy of 1% tenofovir gel formulated as a topical agent for intravaginal application (a microbicide), with coitally dependant dosing (before and after sex). Tenofovir is an ARV drug also used in HIV treatment. The study showed 39% efficacy which increased stepwise in participants who used the gel as directed (Abdool Karim et al 2010). This approach awaits results of a confirmatory trial, as the trial was designed as a 'proof of concept' study and lacked the statistical power for regulatory approval. Only months later, results from iPrEX were published, showing that combination

[1] Tenofovir gel works at a biological level as a form of topical pre- and post-exposure prophylaxis, but as taking an oral tablet is distinct from inserting a vaginal gel, the gel form and the oral form are usually seen as separate strategies.

tenofovir/FTC in tablet form (PrEP) reduced HIV acquisition by 44% in a population of men who have sex with men (MSM) and transgender women who have sex with men at high risk of HIV. Again, efficacy increased stepwise with good adherence to the study product to more than 90% (Grant et al 2010; Anderson et al 2012). Further evidence regarding tenofovir/FTC as PrEP came in 2011 from two trials in heterosexual people in Africa. The Partners PrEP study showed a 75% reduction in HIV incidence in couples where one partner was HIV negative and the other positive (serodiscordant couples), with tenofovir-only PrEP showing a 67% reduction (Baeten et al 2012). Finally the TDF2 study, which tested combined TDF/FTC PrEP conducted in heterosexual men and women in Botswana, showed a 62% reduction in HIV acquisition (Thigpen et al 2012).

In addition, a study testing the efficacy of early[2] ARV treatment for the HIV positive partner in serodiscordant couples (a strategy known as 'treatment-as-prevention') reduced HIV acquisition be a striking 96% (Cohen et al 2012).

These successes in ARV-based prevention sit alongside three randomised controlled trials which have shown that male circumcision can reduce HIV acquisition in heterosexual men by around 50% (Auvert et al 2005, Bailey et al 2007, Gray et al 2007), and a single vaccine trial that showed a modest 26% reduction in HIV acquisition (Rerks-Ngarm et al 2009).

[2] ARV treatment is defined as 'early' when it is administered in people whose CD4 cell levels are above 350.

This block of evidence means that HIV prevention has now advanced well beyond behavioural and barrier modalities alone, and this has ethical implications for the design of future studies.

Alongside the positive efficacy results, however, both PrEP (tenofovir alone and tenofovir/FTC) and tenofovir gel did not protect participants in the Fem-PrEP or VOICE trials, due to poor adherence (Van Damme et al 2012, MTN 2013). This suggests that there is still work to be done to establish an optimal prevention strategy that will be acceptable and usable for women at high risk of HIV acquisition.

Standard of Care and study design

'Standard of care' means the level of care provided to participants in a clinical trial. In HIV prevention trials, it can be used to describe four different aspects of care. Firstly, there is the 'standard of prevention', which is the risk-reduction package provided to all participants in the trial.[3] Secondly, 'standard of care' may be used to refer to the care provided to participants randomised to the comparator arm of a trial (van der Graff and van Delden 2009). Thirdly, there is ancillary care – health care that is provided to trial participants that is indirectly associated with the research, such as contraception and reproductive health care, cervical cancer screening and treatment for illnesses that arise during trial participation (Richardson 2007; Belsky and Richardson 2004). Finally, there is access to ARV for trial participants who acquire HIV on the trial (Macklin 2006).

[3] This term was coined in 2007 in the UNAIDS Ethical Considerations document to end the confusion caused my multiple meanings of 'standard of care'.

Both the standard of prevention (the care provided to all participants) and the choice of a comparator arm (the standard of care against which an experimental intervention is measured), have profound impact on the design of HIV prevention studies. For reasons of efficiency and cost-effectiveness, HIV prevention studies are conducted in populations of high HIV incidence (and these populations are usually in specific geographic areas), because this allows an expeditious answer to the research question. The studies need to enrol sufficient numbers of people to provide a statistically significant result, calculated using the background HIV incidence. The introduction of a highly effective standard of prevention – such as treatment-as-prevention, which has been shown to reduce HIV acquisition by 96% – would require such exponential expansion of the sample size as to make a trial impracticable.[4] For this reason, and because it is hard to justify withholding such an effective intervention in a study setting, it is likely that HIV prevention research targeting the specific population of serodiscordant couples will cease, and the focus fall on others at high risk of HIV acquisition. This article will therefore focus on people at high risk of HIV acquisition who are not in long-standing serodiscordant sexual partnerships.

The guidelines

There are several guidance documents that are relevant to the standard of care issue in HIV prevention trials.

[4] It could be argued that given such an effective intervention, the time has come to stop testing new approaches and to fully fund the global roll-out of early treatment for all people with HIV. This approach does not satisfy the requirement for HIV negative people at high risk to be able to protect themselves, however, and research is likely to continue until this need has been met.

The Declaration of Helsinki is a general guide to research ethics produced by the World Medical Association (WMA 1964; as amended in 2008), an international non-profit association of voluntary national medical associations formed in 1947. The Declaration drew upon the 10 points articulated in the Nuremberg Code and tied them in with physicians' obligations under the Declaration of Geneva (1948). It has since been revised six times, most recently in 2008.

The Declaration states in clause 6 that 'In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests'. Clause 32 goes on to address standard of care specifically:

> *The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:*
>
> *The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or*
>
> *Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.*

Thus the Declaration of Helsinki adopts a universalist position that prescribes a best current standard for research participants in all cases where the risk is serious or irreversible, such as the risk of HIV acquisition.

The International Ethical Guidelines for Biomedical Research Involving Human Subjects adopts a more pragmatic position. These guidelines were developed by the Council for International Organizations of Medical Sciences (CIOMS) in 1993, and revised in 2002. They were intended to assist developing countries to define national policies on the ethics of biomedical research involving humans, to apply ethical standards in local circumstances, and to establish or improve ethical review mechanisms. The CIOMS guidelines offer extensive commentary on the issue of standards of care in general and whether or not an active comparator or a placebo control may be used. The actual guideline (#11) is strict about the use of placebo were an established intervention exists, but it does not insist on the active comparator being the 'best'. Rather, it has to show *some* efficacy, allowing for the use of lower standards – or more technologically appropriate interventions – in specific instances, rather than a universal best practice. Guideline 11 states:

> *As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or ''no treatment''*
>
> *Placebo may be used:*
>
> - *when there is no established effective intervention; when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;*

- *when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.*

The CIOMS guideline is less prescriptive than the Declaration of Helsinki's clause 32 in that 'an established effective intervention' may be a local standard whereas the 'best current proven intervention' calls for an optimal standard. The gap between the two becomes apparent when considering the HIV prevention context: in a prevention trial in heterosexual serodiscordant couples, for example, the CIOMS guidelines would permit condom-based prevention only, while the Declaration of Helsinki could be used to argue for condom-based prevention, plus PrEP for the negative partner, early treatment for the positive partner, and access to male circumcision for HIV-negative male partners.

In addition to these general research guidelines, there are two set of ethical guidelines that deal specifically with HIV prevention trials, the UNAIDS Ethical Considerations in HIV Biomedical Prevention trials (updated in 2012) and the HIV Prevention Trials Network Ethics Guidance for Research (2009). These documents are complementary in some respects but they differ in the way that they outline the obligations regarding standards of prevention and care.

Guidance point 13 of the UNAIDS document, on standards of prevention, stipulates that there is an obligation to provide:

> *…access to all state of the art HIV risk reduction methods … to participants throughout the duration of the biomedical HIV prevention trial. New HIV-risk-reduction methods should be added, based on consultation among all research*

stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.

Like the Declaration of Helsinki, the UNAIDS/WHO guidance takes a universalist perspective, prescribing state of the art prevention interventions as standard of prevention. Morally relevant criteria, including scientific validation, approval by normative bodies and the impact on research feasibility, may influence whether or not a new modality is considered standard of prevention.

In addition to addressing standard of prevention, it also stipulates standards for ancillary care, specifically reproductive health care, treatment for sexually transmissible infections (STIs) and programs to address domestic violence.

Guidance point 15 of the UNAIDS document, on the control arm, supports point 13 by reiterating that "participants in both the control arm and the intervention arm should receive all established effective HIV risk reduction measures". In other words, experimental new interventions should be layered on top of what is already known to work. The allowable exceptions mentioned include instances where there is a sound biological rational for considering that an intervention shown effective in one population cannot be generalised to another, such as a vaccine tested against a particular subtype, or a product tested vaginally that cannot be extrapolated to rectal use.

The HPTN Guidance takes a different approach these issues. To begin with, it distinguishes between an ethical obligation and an ethical aspiration. Guidance point 9 on the standard of prevention identifies the provision of an effective prevention

package for trial participants as obligatory. The *content* of that package, however, is undefined except insofar as there must be established evidence of efficacy and the prevention interventions must be practically achievable and reasonably accessible in the trial setting. Using this framework, in settings where particular risk reduction methods are deemed culturally inappropriate or illegal, they need not be offered so long as some other effective form of prevention is offered. Provision of voluntary medical male circumcision or needle exchange programs are not required under these guidelines even if trials enrol HIV negative uncircumcised men or injecting drug users, if these are not reasonably available in local communities[5].

The HPTN document also provides guidance on aspects of research not detailed in the UNAIDS document, including specifying processes of community engagement, building capacity and partnerships, and attention to ancillary care.[6] Importantly, a new category of people to whom researchers have obligations is introduced – the 'screened out'. These are people who volunteer to participate in prevention trials but are found ineligible for reasons such as pre-existing undiagnosed HIV infection.

In addition to these two sets of guidelines, there is a set of consensus points developed by a group of HIV prevention researchers and bioethicists in 2009 that require consideration, from the 'Standard of Prevention' consultation in Uganda (McGrory et al 2010). These consensus points articulate that a new intervention is considered 'state

[5] While in-depth discussion of these issues are beyond the scope of this paper, conducting a trial in an area where participants are denied access to a proven safe and effective intervention for social or political reasons is both inappropriate and exploitative.

[6] UNAIDS deals with community engagement processes in detail in a separate document co-authored by UNAIDS and AVAC, the Good Participatory Practice Guidelines, first published in 2007.

of the art' when it is approved by a relevant regulatory authority or included in normative guidelines. They also stipulated that there was a strategic set of trials using PrEP in different populations that should be allowed to continue without alteration, regardless of whether early results showed efficacy, in order to get maximum information about PrEP in different populations.

The UNAIDS and HPTN documents will be discussed in detail in this chapter.

Key differences

The HPTN document was developed specifically to meet the needs of a research network undertaking HIV prevention work. It defines itself as 'pragmatic' rather than idealistic in its approach, and sets out to address 'limitations, gaps and inconsistencies' perceived in existing guidelines. It is structured to address issues that arise sequentially from before the trial to its aftermath, and it identifies which stakeholders are responsible for implementing which guidance points as well as defining the strength of guidance as 'obligatory' or 'aspirational', as noted above. In addition, it specifies a limited conception of justice in its underpinning principles – 'social justice', defined as "the ethical concerns related to treating people equally, avoiding exploitation, and trying to reduce health disparities" (Rennie and Sugarman 2010). Defining and limiting justice in this way prioritises equality between trial participants and their local communities rather than aiming to reduce health disparities between trial participants in high income countries and those in low and middle income countries.

While the UNAIDS guidelines impose duties on researchers to adopt international best practice, the HPTN document allows a looser standard to be adopted. The rationale for this is threefold: 'state-of-the-art' risk reduction methods that are not available outside the trial could constitute undue inducement to participate; to prevent research practices that would compromise 'real world' significance of data; and to guard against people within a trial having access to a higher standard of prevention than those outside it; (Rennie and Sugarman 2010). The focus on current local capacity reframes the discourse about double standards, generally understood to mean disparities between high income countries and developing countries, to one that centres on the local research community.

This brings us to the crux of the difference between the two sets of guidelines. With the FDA now having approved PrEP for HIV prevention, under the UNAIDS guidelines there is a prima facie requirement to provision PrEP as standard of prevention, as PrEP clearly meets the definition of 'state-of-the-art', having been approved by a normative body. Were this to occur, it would require much larger, more expensive and highly complex trials for subsequent experimental interventions – but these trials could dramatically decrease HIV acquisition in the trial populations. An argument against a 'state-of the art' PrEP-containing prevention package is that it could create serious inequities between trial participants and their communities in which PrEP is not available, though this could be rebutted on the ground that such provision would be a capacity building-enabler of better services in communities. Sustainability of the intervention is also an issue.

Under the HPTN guidelines, no such change is required, as these guidelines define a minimum standard that is amenable to ongoing research studies using the currently established standard of prevention (i.e. condoms, behavioural counselling and treatment for sexually transmissible infections), despite the fact that in the communities that have high HIV incidence, the inadequacy of existing methods is arguably well established. There is a clear tension between the imperative to protect participants and the imperative to find a cheap, effective user-friendly HIV prevention technology. Who gains from such studies is an important consideration – people in high incidence populations in low and middle income countries, or those in high income countries?

The mother-to-child transmission controversy revisited

These questions revisit the debate from the late 1990s about alleged doubled standards in mother-to-child prevention trials. A major ethical controversy erupted in 1997, when an article in the *New England Journal of Medicine* called into question placebo-based trials for mother-to-child HIV prevention in Africa and Asia, despite a proven effective intervention being published in 1994.The critics pointed out that the placebo-controlled trials violated the Declaration of Helsinki. They alleged that an unacceptable double standard regarding research ethics was operating, reminiscent of the notorious Tuskegee trial (Angell 1997; Lurie and Wolf 1997). Defenders of the trials argued the ‘standard of care’ established in the 1994 was not feasible in developing countries, that the placebo-based trials addressed a significant public health issue in those countries, and that the question that needed to be answered was whether the experimental therapy was better than nothing, not whether it was as good as an unattainable standard (Varmus and Satcher 1997).

The controversy led to a redrafting of the Declaration of Helsinki, but in the end the revised version(s) maintained that new interventions for serious conditions should not be tested against placebo when established treatment exists. Regardless of this outcome, bioethicists and researchers remain polarised on this issue (Macklin 2001). With respect to HIV prevention, the debate has slumbered as provision of behavioural and barrier prevention has been accepted by researchers and communities alike, and until very recently circumcision was the only proven biomedical intervention, which has a very specific population (heterosexual men) and is subject to profound social and cultural mores (Macklin 2008). The advent of ARV-based prevention reignites the issues.

Practical aspects

Amidst philosophical disagreement about standards, a focus on consensus-building processes among stakeholders including communities and actual and potential trial participants has emerged as a means for getting broad agreement of how research should be conducted in particular settings (for example, Vallely et al 2007). In 2007 UNAIDS and AVAC developed Participatory Practice guidelines (revised in 2012) that detail expected engagement with communities and the setting up of mechanisms that give communities opportunities for input throughout the research.

This is a very significant move, catalysed by the premature closure of PrEP trials in the early 2000s that were perceived to have been insufficiently consultative with trial communities, and which were perceived to be not sufficiently responsive the participants' needs (Forbes and Mudaliar 2009; Haire 2011; McGrory et al 2009; Ukpong and Peterson 2009).

Direct two-way communication with communities and giving community stakeholders real power to influence aspects of the research is a very important development. Community members do not meet with international researchers on an equal basis, however: there are vast power differentials at play. Indeed, the relationship has been defined as one of structural inequality, such that the researcher has a fiduciary responsibility to the research participant (Miller and Weijer 2006). Accordingly, while community collaboration with HIV prevention research is essential for best practice, it is no substitute for clear standards.

Making the call

The evidence that treatment-as-prevention, circumcision and PrEP are effective in preventing HIV acquisition means that it is no longer ethically appropriate to design HIV prevention without securing access to these interventions. Each of these strategies has been approved by a regulatory authority or in a normative guideline (the WHO in the case of circumcision, the International Antiviral Society, USA panel in the case of treatment-as-prevention, and the FDA in the case of PrEP).

Despite the recent advances in biomedical prevention, however, the need to develop new interventions remains. Longer-acting products in particular are required to avoid the problem of suboptimal adherence. A balance therefore needs to be struck between prioritising the protection of trial participants and facilitating ongoing research into new HIV prevention technologies that might be cheaper, more effective and more feasible in low- and middle-income countries.

Several different solutions have been proposed for the design of future prevention trials. Firstly, PrEP could be added into the standard of prevention and made available to all trial participants, who would be randomised to receive the experimental intervention or placebo on top of this background. The advantage of this is that it would be highly likely to reduce HIV acquisition very significantly in the trial population. The problem is that it would require very large sample sizes to obtain a result, and it might be difficult to untangle the efficacy (or not) of the experimental intervention from PrEP efficacy (which would likely be affected by differential adherence, as in trials to date).

A variation on this approach would be to allow PrEP in standard of prevention packages only where it is available in the community – namely, the US and at PrEP demonstration sites[7] – and not in other trial sites. There are serious objections to this. If the trial were only conducted in sites where PrEP was available, the same problems with very large sample size and difficulty in discerning the impact of the experimental intervention would apply. If some sites had PrEP access and others did not, a stark double standard would be in evidence, with the majority of HIV seroconversions likely to occur in the non-PrEP sites.

Alternatively, new trials could seek volunteers from amongst those who opt not to take PrEP, who could thus be randomised to experimental intervention or placebo. If it were the active choice of the volunteers not to take PrEP, there could be no ethical

[7] At the time of writing, the only demonstration sites launched were in the US, with others planned in two or three cities in Brazil.

objection. There are two problems with this, however. Firstly, in order for the choice to opt out of PrEP to be free, these studies would need to take place in setting where PrEP is available, which is a major constraint. Secondly, available research suggests that people who recognise themselves to be at high risk of HIV acquisition tend to be amenable to taking PrEP (Wheelock et al 2013, Holt et al 2011). People who don't wish to take PrEP may therefore be at lower risk, which would then require larger sample sizes to get a result, with the risk of a futile result.

Finally, there is the option of using PrEP as the active comparator. Again, there are several issues here. For this to be ethical, there would need to be strong preliminary evidence to suggest that the experimental intervention would be of comparative efficacy, so as to ensure equipoise (i.e. uncertainty as to whether one arm would be better than the other) between the two arms of the trial. The scientific objection to using PrEP as a comparator is the lack of precision regarding the preventative efficacy of TDF/FTC, with point estimates from randomised control trials ranging from 6% (FEM-PrEP) to 75% (Partners PrEP). An active comparator is usually required to have a substantial magnitude of effect, precisely estimated, with that estimate relevant to the trial population (Fleming 2013). This is not an insurmountable barrier, however. Further analyses of high adherers from iPrEx have shown efficacy of around 90% (Anderson et al 2012). Regrettably, similar information is not yet available regarding high adherence in women. Further, the requirement for a 'precise estimate' is questionable in this context, given that it has been well established that PrEP reduces HIV acquisition significantly when it is taken, but its effectiveness is attenuated by poor adherence (Mayer 2013). A long-acting intervention that had lower biological efficacy might work better than PrEP in one population and worse in another, more adherent one. Head-to-head studies are an opportunity to discover this.

Active comparator studies using PrEP also offer an opportunity to study further factors that relate to adherence in specific populations, and potential strategies for improvement.

PrEP is the appropriate comparator because there is good evidence that it works if people adhere to it. Adherence is a significant issue (Van Damme et al 2012; Beaten et al 2012), however, as is cost. It is not ideal, but in combination with existing barrier methods it is the best technology available for HIV negative women or men who have receptive sex. Finding an intervention that works as well as PrEP without requiring daily adherence would be a breakthrough. If a new experimental intervention failed to be as good as PrEP, then the trial would still be useful for getting further information about PrEP adherence in settings where HIV is hyper-endemic.

Voluntary circumcision for HIV negative heterosexual men should be offered as standard of prevention in studies that include this population, as it is feasible and cost-effective. Uptake of this option is likely to differ according to social and religious factors, but HIV negative heterosexual male participants in research studies should be allowed to make up their own minds, based on the evidence of safety and efficacy and their own personal values as to whether it is appropriate for them. The option should not be censored on the presumption of unilateral social and religious values in a community.

The recommendation to use PrEP as an active comparator arm, with circumcision offered as appropriate as standard of prevention, applies to trials that are in design phases. It would be counterproductive, for example, to try to add extra arms to trials

like FACTS 001, which is designed to meet the requirement of the South African regulatory authorities, and without which the question of how effective tenofovir gel is may never be answered comprehensively. Continuation of this trial should be supported for this reason. The continuance of PopART should also be supported, as this is a cluster trial testing an approach to the implementation of circumcision and treatment-as-prevention in a series of communities. PopART is not testing an experimental technology, but a particularly intensive approach to engaging people with proven HIV prevention practices, male circumcision and treatment-as-prevention.

Conclusion

In the absence of a universally acceptable, highly effective, cheap and user-friendly vaccine, HIV prevention research will continue to be an important component in the struggle to eliminate HIV. Despite its seemingly high biological efficacy, TDF/FTC PrEP is far from an ideal intervention, particularly given the serious problems with adherence shown in several of the trials to date. Even if adherence can be improved significantly in high-incidence populations through specialised programs, a short-acting user-dependent prevention technology is vulnerable to a range of potential disruptions. For people who are at high risk of HIV acquisition (from risk factors other than a serodiscordant regular sex partner), however, PrEP is the best adjunct to barrier and behavioural prevention that we have. Certainly there needs to be better data on how to use it optimally, but this can be gathered in studies that use PrEP as a comparator against which other experimental interventions are tested.

The goals of HIV prevention research must be to find the most effective ways of using existing tools, including PrEP, and to establish the effectiveness of new tools.

Randomised controlled trials are an important part of this, but they need to be designed in such a way as to ensure that all participants receive effective interventions, even though this necessarily means that trials will need larger sample sizes. HIV prevention trial participants are among the most vulnerable to HIV in the world, and need to be protected.

Incorporating TDF/FTC PrEP as the comparator arm in forthcoming HIV prevention trials balances the need for ongoing research with appropriate protection for research subjects. While a daily tablet is not an ideal prevention intervention, as it is vulnerable to stock-outs and to individual forgetfulness, it has the advantages of being separable from each sex act and appropriate for receptive sex partners. For HIV negative people at high risk of HIV acquisition, it is the best protection currently available. If we take seriously the moral imperative to address HIV incidence in those populations most vulnerable to HIV acquisition, then PrEP needs to be the comparator in forthcoming research.

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References

Angell, M. 1997. The ethics of clinical research in the third world. *New England Journal of Medicine* 337 (12):847-849.

Auvert, B., D. Taljaard, E. Lagarde, J. Sobngwi-Tambekou, R. Sitta, and A. Puren. 2005. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLoS Med* 2 (11):e298.

Bailey, R.C., S. Moses, C.B. Parker, et al. 2007. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *The Lancet* 369:643 - 656.

Abdool Karim Q., S. S. Abdool Karim, J. A. Frohlich,et al. 2010. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 329 (5996):1168-1174.

Baeten, J. M., D. Donnell, P. Ndase, et al. 2012. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine* 367 (5):399-410.

Belsky, L., and H. S. Richardson. 2004. Medical researchers' ancillary clinical care responsibilities. *British Medical Journal* 328 (7454):1494-1496.

Cohen, M. S., Y. Q. Chen, M. McCauley, et al. 2011. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine* 365 (6):493-505.

Fleming, T. 2013. Non-inferiority clinical trials. Some key consideration in PrEP and microbicide studies. Presentation at the meeting on the Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues, Washington, January 7 2013.

Available at: http://www.hivforum.org/storage/hivforum/documents/FutureofPrEP/session_2_fleming.pdf Accessed February 1, 2013.

Food and Drug Administration. (FDA). 2012. FDA Approves First Drug for Reducing the Risk of Sexually Acquired HIV Infection. (News release) July 16 2012. Silver Spring, MD: FDA. Available at:

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm (accessed September 10, 2012).

Forbes, A., S. Mudaliar. 2009. Preventing Prevention Trial Failures: A Case Study and Lessons Learned for Future Trials from the 2004 Tenofovir Trial in Cambodia Washington: Global Campaign for Microbicides.

Grant, R. M., J. R. Lama, P. L. Anderson, et al. 2010. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *New England Journal of Medicine* 363 (27):2587-2599.

Gray, R.H,. G. Kigozi, D. Serwadda, et al. 2007. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 369:657 - 666.

Haire, B. G. 2011. Because we can: Clashes of perspective over researcher obligation in the failed PrEP trials. *Developing World Bioethics* 11 (2):63-74.

Holt M., D.A. Murphy, D. Callander, et al. Willingness to use HIV pre-exposure prophylaxis and the likelihood of decreased condom use are both associated with unprotected anal intercourse and the perceived likelihood of becoming HIV positive among Australian gay and bisexual men. *Sexually Transmitted Infections*. 2012; 88:258–63.

Knox, R. and M. Doucleff. 2012. Clinton Reveals Blueprint For An 'AIDS-Free Generation'. *Shots: Health News*. http://www.npr.org/blogs/health/2012/11/29/166154269/clinton-reveals-blueprint-for-an-aids-free-generation.

Lurie, P., and S. M. Wolfe. 1997. Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries. *New England Journal of Medicine* 337 (12):853-856.

McGrory, E., A. Irvin, L. Heise. *Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site. Washington, DC: Global Campaign for Microbicides at PATH; 2009. Available at: www.globalcampaign.org/clientfiles/Cameroon.pdf (accessed: 8 January 2011).*

Macklin, R. 2001. After Helsinki: Unresolved Issues in International Research. *Kennedy Institute of Ethics Journal* 11 (1):17-36.

Macklin, R. 2006. Changing the Presumption: Providing ART to Vaccine Research Participants. *The American Journal of Bioethics* 6 (1):1 - 5.

Macklin, R. 2008. Standard of care: an evolution in ethical thinking. *The Lancet* 372 (9635): 284-285.

McCormack, S. Perspectives of a clinical researcher at the stage of grant writing. Standards of care in Future Microbicides Research Symposium. Presentation at the M2012 symposium. Microbicide 2012, Sydney, Australia. April 15th to 19th, 2012.

May M., M. Gompels & C. Sabin. 2012. *Life expectancy of HIV-1-positive individuals approaches normal, conditional on response to antiretroviral therapy: UK collaborative HIV cohort study.* Eleventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract O133, 2012.

Mayer, K. 2013. Future of PrEP and Microbicide Research: Setting the Stage. Presentation at the meeting on the Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues, Washington, January 7, 2013. Available at:

http://www.hivforum.org/storage/hivforum/documents/FutureofPrEP/session_1_mayer.pdf (accessed February 2, 2013).

Microbicide Trials Network. (MTN). 2013. Understanding the results of VOICE. Available at: http://www.mtnstopshiv.org/news/studies/mtn003 Accessed 12 March 2013.

Miller, P.B., and C. Weijer. 2006. Fiduciary Obligation in Clinical Research. *The Journal of Law, Medicine & Ethics* 34 (2):424-440.

Philpott, S., K. West Slevin, K. Shapiro and L. Heise. 2010. Impact of Donor-imposed Requirements and Restrictions on Standards of Prevention and Access to Care and Treatment in HIV Prevention Trials. *Public Health Ethics* 3 (3):220-228.

Philpott, S., L. Heise, E. McGrory, L. Paxton, C. Hankins, and the participants in the GCM/CDC/UNAIDS Consultation on Standards of Prevention in HIV Prevention Trials. 2011. The challenge of defining standards of prevention in HIV prevention trials. *Journal of Medical Ethics* 37 (4):244-248.

Rennie S., J. Sugarman and the HPTN Ethics Working Group. 2009. HIV Prevention Trials Network Ethics Guidance for Research. HIV Prevention Trials Network. Available at: http://www.hptn.org/web%20documents/EWG/HPTNEthicsGuidanceV10Jun2009.pdf (accessed July 31, 2012).

Rennie, S., and J. Sugarman. 2010. Developing ethics guidance for HIV prevention research: the HIV Prevention Trials Network approach. *Journal of Medical Ethics* 36 (12):810-815.

Rerks-Ngarm, S., P. Pitisuttithum, S. Nitayaphan, et al. 2009. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *New England Journal of Medicine* 361 (23):2209-2220.

Richardson, H. S. 2007. Gradations of Researchers' Obligation to Provide Ancillary Care for HIV/AIDS in Developing Countries. *American Journal of Public Health* 97 (11):1956-1961.

Thigpen, M. C., P. M. Kebaabetswe, L. A. Paxton, et al. 2012. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *New England Journal of Medicine* 367 (5):423-434.

Ukpong, M., and K. Peterson, eds. 2009. *Oral Tenofovir Controversy II: Voices from the Field*. Falomo, Nigeria: New HIV Vaccines and Microbicides Society (NHVMAS).

UNAIDS. 2011. Good participatory practice: Guidelines for biomedical HIV prevention trials 2011. 2nd ed. Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf (accessed February 2, 2013).

UNAIDS. 2012. *Global report: UNAIDS report on the global AIDS epidemic 2012*. Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at:

http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf (accessed January 30, 2013).

UNAIDS/WHO. 2012. Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS/WHO Guidance Document. (English original 2007, additional guidance point added 2012). Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO). Geneva: UNAIDS and World Health Organization. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf (accessed January 14, 2013).

Vallely, A., C. Shagi, S. Kasindi, et al. 2007. The benefits of participatory methodologies to develop effective community dialogue in the context of a microbicide trial feasibility study in Mwanza, Tanzania. *BMC Public Health* 7:133.

Van Damme, L., A. Corneli, K. Ahmed, et al. 2012. Preexposure Prophylaxis for HIV Infection among African Women. *New England Journal of Medicine* 367 (5):411-422.

van der Graaf, R., and J. J. M. van Delden. 2009. What is the Best Standard for the Standard of Care in Clinical Research? *The American Journal of Bioethics* 9 (3):35-43.

Varmus, H. and D. Satcher. 1997. Ethical Complexities of Conducting Research in Developing Countries. *New England Journal of Medicine* 337 (14):1003-1005.

Wheelock, A., A. B. Eisingerich, J. Ananworanich, et al. 2013. Are Thai MSM Willing to Take PrEP for HIV Prevention? An Analysis of Attitudes, Preferences and Acceptance. *PLoS ONE* 8 (1):e54288.

World Medical Association. 2008. *Declaration of Helsinki*, amended. Originally published 1964. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html Accessed February 6, 2013.

World Medical Association. 1948. *Declaration of Geneva*. Available at: http://en.wikipedia.org/wiki/Declaration_of_Geneva (accessed February 6, 2013).

Part 4, Chapter 1

Summary and conclusions

Summary and conclusions

Broad aim of this thesis

The broad aim of this thesis was to explore the ethical issues relating to the standards of care in HIV biomedical prevention research, with a specific focus on how benefits for participants are negotiated. It had empirical and normative components. The empirical component was a mixed-methods study that surveys principal investigators of HIV prevention trials and the ethics committees that review them, and in-depth interviews with principal investigators of HIV prevention trials. The normative component first explored the moral basis for ARV-based prevention in the absence of true universal access for treatment and then examined how debates on standards of care apply in the evolving context of partially effective HIV prevention interventions.

The study took place at a dynamic period of HIV prevention research. Between 2009 and 2012 positive efficacy results were reported from six large, randomised controlled trials (RCTs) of HIV prevention interventions. One of these trials tested a candidate vaccine, while the other five tested three different, but related, preventive strategies that use antiretroviral drugs in different ways: topical use (a vaginal microbicide); pre-exposure prophylaxis using either tenofovir alone or emtricitabine/tenofovir combined; and treatment-as-prevention (treating HIV positive people with ARV earlier than medically required in order to prevent transmission to sexual partners). These trials added to existing evidence that medical male circumcision is partially effective in preventing HIV infection.

Alongside these positive efficacy results, the results of the FEM-PrEP and VOICE trials were reported. These demonstrated the importance of adherence in trials of user-dependent technologies. Neither trial showed efficacy, and subsequent studies revealed that less than a third of participants were taking their drugs, as shown by blood level analysis (Van Damme et al 2012; Microbicide Trials Network 2013). Added to the lower-than ideal adherence in iPrEX (Grant et al 2010), these trials signal that adherence is the next big issue in HIV prevention research. This will impact on the conduct of future HIV prevention research by increasing sample sizes, by imposing directly observed therapy, or by discouraging the research and development of daily use products.

Key empirical findings

This thesis has several key empirical findings. Firstly, there is no consensus as to how standards of prevention should change in response to emerging partially effective interventions. While some investigators argue that new experimental interventions should be tested against optimised background prevention, others are adamant that prevention options for trial participants should not exceed those available to community members outside the trial. Some investigators argue that optimised prevention within trials will ensure that trials require larger sample sizes, and hence the benefits of participation shared amongst larger populations; others argue that that basic prevention packages are sufficient and that these benefit the HIV prevention endeavour by expediting research results.

With regard to implementing new research findings, investigators had significantly different approaches as can be seen most clearly with the example of medical male

circumcision. One research group proactively added voluntary male circumcision to standard of prevention based of the strength of the data, others had information and referral processes that worked with national guidelines, but one major study had no systematic approach to the issue at all.

Controversy over provisions of ARV for seroconverters, however, has vanished. The exponential growth of ARV access programs, both nationally based and donor-funded, and successful partnerships between access programs and research sites have made access to care for seroconverters the norm.

Investigators saw it as necessary, for both ethical and practical reasons, to provide some level of ancillary care that complemented other local health services. This sometimes created ethical conflict due to constraints of either funding or local infrastructure. With the emphasis on delivery of ancillary care, researchers generally described their focus broadly in terms of having a beneficial impact on individuals and communities, rather than a narrow focus on simply answering a research questions. Even so, the best medical interests of individual participants were generally not the key priority for the informants, but one factor to be balanced with several others. The competing factors included the scientific integrity of the trial, limitations imposed by funders, and the constraints of local infrastructure.

Regarding post-trial access, each of the nine HIV prevention trials that had positive efficacy results had undertaken access planning in the event that their trial produced an effective intervention. This suggests that post-trial access is considered normative.

Differences were evident however in the mechanisms for providing access, the timeframes in which this was achieved, and the length of time it was sustained. The surprising aspect of the post-trial access is firstly that the key mechanism for delivering it is, in fact, a clinical trial, so it is actually a form of intra-trial rather than post trial access. Cross-over mechanisms (where participants on placebo are switched to active drug) appear to offer major advantages in terms of timeliness over new formal extension trials that can take months or years to get the necessary approvals. Secondly, even though the obligation to provide access is a shared one in which investigators have only a limited role, the advocacy efforts of investigators appear to be very important for securing access, particularly when there might be issues in securing population-wide regulatory approval.

Finally, the reported duration and depth of community engagement and consultation increased over time, with later trials generally entailing more community engagement from earlier stages of the research process.

Key normative findings

Moral basis for ARV as prevention

In Chapter 1, *Ethics of ARV-based HIV prevention* I argue that there is a sound moral basis for using ARV for prevention, even though some seven million people who need treatment for their health do not have access to it. Firstly I propose that that HIV risk is largely determined by structural factors – the HIV prevalence in the demographic pool in which one has sex rather than individual behaviour. Secondly, while the acquisition of HIV is preventable through the use of condoms and behavioural

strategies such as celibacy or mutual monogamy, these strategies are of limited usefulness in many circumstances.

Using two different ethical frameworks – principle-ism and a public health stewardship framework – *Ethics of ARV-based HIV prevention* considers both treatment-as-prevention and PrEP.

Treatment-as-prevention involves treating people with HIV earlier than would be required to maintain their own health for the purpose of reducing their infectivity to sexual partners. It has the potential advantage of offering as yet speculative health benefits to the positive person, but also exposes him or her to the known risks that come with longer term-exposure to ARV. This includes drug toxicities, and perhaps more importantly, the risk of drug resistance developing if adherence is inadequate, which could compromise later treatment options. Treatment-as-prevention approaches have been criticised for prioritising a public health benefit (i.e. the suppression of viral replication, reducing infectivity) over the health of the patient, potentially leading to coercive regimes of testing and treatment without informed voluntary participation.

PrEP on the other hand requires HIV negative people to take ARV for preventive purposes, but is the first preventive intervention directly under the control of individuals at risk of HIV who have receptive vaginal or anal sex. As such it offers a new prevention modality for population that is at highest risk of HIV acquisition – young women in southern Africa.

Ethics of ARV-based HIV prevention argues that each strategy has risks and benefits, but that each has a place in the epidemic. One enables the person with HIV to be less infectious to partners, while the other enables highest risk populations in the world to protect themselves through a strategy that empowers them to be proactive on their own behalf, not one that positions them as hapless (or lucky) recipients of a fate determined by others' actions.

How good is good enough?

In Chapter 2 *How good is 'good enough'?* my co-authors and I argue that the standards of evidence required for licensure applied to tenofovir gel and tenofovir/emtricitabine PrEP may be inappropriate measures of how useful new modestly effective HIV prevention products might be in the generalised epidemics in southern Africa. We argue that reducing the incidence of HIV is both a public health priority and a moral imperative, and question the need for lengthy confirmation trials before licensure.

As new biomedical products of moderate efficacy have the potential to significantly slow the epidemic in these affected countries, delay in introducing effective prevention strategies may result in hundreds of thousands of potentially avoidable infections. We therefore ask on what basis was it decided a) that the two new trials do not provide sufficient evidence to support these products being made available outside research settings, and b) that they should not form part of the standard of care in the control arm of new trials, and replace placebos. Setting the evidentiary bar high facilitates ongoing placebo-controlled trials, which makes research cheaper and more efficient. Faster research *might* result in finding more effective product more quickly. However there is no guarantee of this and, as we argue, it entails a substantial human cost.

The key point about CAPRISA 004 and iPrEx is that different decisions could reasonably be made both regarding licensure and roll-out of the products in some areas where HIV is endemic, and in the composition of 'standard of prevention' in subsequent trials. For example, the South African regulators could have decided that, given South Africa's high HIV incidence in women, licensure of tenofovir gel was justified (presumably with some follow-on open label studies to gather more data). While the failure of VOICE gives pause for thought, the low adherence to all study products in that trial suggests that there was something specific in that population context that dramatically affected adherence, rather than an efficacy issue per se. If the 39% efficacy rate of CAPRISA 004 translated into real-world effectiveness it could have prevented 100,000 new infections per year.

Standard of Prevention

Chapter 3, on the standard of prevention, discusses the issues that arise in considering appropriate standards in the light of evolving evidence.

Antiretroviral (ARV) drugs can be used in diverse ways to reduce HIV acquisition or transmission risks, taken either as pre-exposure prophylaxis (PrEP) by those who are uninfected, or as early treatment for prevention (T4P) by those living with HIV. This expands the armamentarium of existing HIV prevention tools. These findings also have implications for the design of future HIV prevention research trials. With the advent of multiple effective HIV prevention tools, discussions about the ethics and the feasibility of future HIV prevention trial designs have intensified. Determining the appropriate trial design and prevention package for a particular study in a specific HIV risk population requires careful consideration, taking account of national and

international guidelines, ARV programme coverage, and the perspectives of researchers, ethics committees, trial sponsors, regulators, communities, and other HIV prevention trial stakeholders. There is currently no documented evidence on consultative decision-making processes for defining the standard of prevention packages for HIV prevention research. The field needs to develop processes that engage all stakeholders in realistic and practical decision-making in a time-sensitive manner, without undue prioritisation of financial considerations above the interests of trial participants.

Time for change

Chapter 4, *It's time*, uses both the evidence form clinical trial and the U.S FDA approval of PrEP to argue for new standards.

In July 2012, based on evidence from two major trials, the United States Food and Drug Administration approved the use of combined oral tenofovir/emtricitabine as pre-exposure prophylaxis (PrEP) for people at high risk of HIV acquisition. PrEP effectiveness is marred by poor adherence, however, even in trial populations, thus it is not a magic bullet for HIV prevention. Inclusion as a comparator also offers unique opportunities to study factors that related to adherence in different populations. Despite the adherence conundrum, PrEP remains the most effective biomedical HIV prevention intervention available for people at high risk of HIV, particularly those who have receptive sex and lack the power to negotiate condom use. Accordingly, there are compelling reasons to compare future experimental HIV prevention interventions against PrEP. Using PrEP as a comparator serves the interests both of trial participants and of scientific research: not only would HIV incidence be reduced,

but also the question of whether new interventions were superior to best proven interventions, in a given setting, would be answered comprehensively.

Situating this study historically

At the beginning of this study (mid-2009) there was a 'practical consensus' about the standard of prevention and care in HIV prevention trials. Condom-based prevention with counselling and STI treatment were the preventative standard, with some form of linkage to care for seroconverters, most often though not always through a separate agency. Access to hormonal contraception – particularly the oral contraceptive pill and injectables – was frequently facilitated or directly provided in studies that included female participants, to avoid pregnancies complicating or confounding the trials (research ethics prevent pregnant women from taking experimental products until there is good safety and efficacy data in other populations). Other forms of ancillary care depended on the sites, the sponsors and the trial populations, and post-trial access to successful intervention was limited to access to voluntary medical male circumcision[1].

This was a 'practical' rather than a true consensus: from approximately 2006, the above had become the standard practices, though differences in implementation could still mean that the levels of prevention and care received by trial participants could differ significantly. Some principal investigators however criticised the level of prevention offered within trials as being too far above the locally available standards

[1] The HIV prevention benefit of voluntary medical male circumcision only applies to HIV negative heterosexually active men living in countries with generalised epidemics.

within trial communities, with better standards of prevention within trial potentially masking the efficacy of some products.

The local standard compared with the best proven first plays out with regard to medical male circumcision, where some trials provide or facilitate provisions proactively, while others await the establishment of government programs.

Two major contextual elements affect the negotiation of benefits for trial participants: the universal access movement for ART, and increasing recognition of the role of community participation and collaboration in HIV prevention research. As discussed in Pt 1 Chapter 2, *Because we can*, four major PrEP trial sites[2] were closed in the early 2000s amidst assertions that the research processes were unacceptable to the communities in which they were to occur. The specific allegations across the sites were of insufficient informed consent practices, a perceived lack of access to ART for seroconverters, inadequate provision of HIV prevention counsellors, no provision for post-trial access, lack of insurance in the event of illness induced by the study drugs and limited involvement of the affected communities in trial design. The closure of these trials focused attention on the importance of community perception and community collaboration for ensuring the successful completion of research. Indeed, it showed that clinical trials could fail at a *social* level, despite being scientifically robust. This resulted in the Good Participatory Practice Guidelines, which provides a

[2] I am referring to 'sites' rather than trials as it's easier to be accurate. Sites were closed in Cambodia, Cameroon, Nigeria and Malawi; Cambodia and Malawi were distinct trials, while Nigeria and Cameroon were part of a larger trial that also had a site in Ghana, which did not close.

guide to community collaboration and addresses the need for access to ART for seroconverters.

As I argue in Pt 1 Chapter 2, *Because we can*, recognition that there is a duty of care or moral obligation to provide access to ART to seroconverters is significant because it broadens the role of research in the developing world. Rather than functioning as a dislocated, disinterested machine for the production of knowledge, this obligation creates a new role for research as part of a capacity building project that can help to redress health disparities. This view is similar to the views published by Soloman Benatar and colleagues (2001; Singer and Benatar 2001; Shapiro and Benatar 2005), in that it recognises an obligation for research projects to play a role advancing social goals more broadly than simply focusing on benefits for participants. It differs from those views in that I consider that the obligation to provide the participant with a universal standard of care – insofar as that is possible – remains. Participant benefits can be the entry point that helps leverage prevention and care services for the wider community. As Macklin argues (2012 personal communication), access has to start somewhere.

By the end of the study in 2013, the focus in HIV prevention has once more swung around toward socio-behavioural issues, with the release of VOICE data on 4 March, 2013. Rather than confirming the efficacy of any of the three intervention it tested, the interventions in VOICE showed no efficacy against HIV, due to the fact that less than

30% of the participants[3] adhered to the trial protocol. This result has once more focused attention on the large-scale clinical HIV prevention trial as a complex social hub involving many different people with different aims, interests and values whose investment in the trial process may be for totally different reasons than those assumed by those who designed the trial.

An interesting side effect of the VOICE result has been increased emphasis upon the original trials (such as iPrEX) that provided evidence of biological efficacy of ARV for prevention in negative people – those very trials that, it was argued, required extensive confirmation. This turn supports the arguments made in Pt 3 Chapter 2, *How good is good enough*, that the initial trials contained enough data on biological efficacy, and hence obviated the need for further placebo controls.

Specific aims of the thesis

The specific aims of the study were:

1. To gather evidence on how benefits to participants are negotiated in efficacy trials of biomedical HIV prevention technologies;
2. To re-consider the debates about obligations to trial participants in the light of the positive trial results (what are the ethical issues in HIV prevention research in the age of partially effective HIV prevention modalities?);

[3] Drug was detected in 29 percent of blood samples from women in the tenofovir/emtricitabine group, 28 percent of samples in the oral tenofovir group and 23 percent among those in the tenofovir gel group.

http://www.mtnstopshiv.org/news/studies/mtn003

3. To understand how principal investigators and ethics committees navigate this territory, and how experience in conducting HIV prevention trials shapes views on how they should be conducted in the future;
4. To explore the factors that affect how and when positive research findings are implemented; and
5. To ask whether there are ethical issues that arise from the empirical research that are not present in the current normative literature.

Aim 1: *To gather evidence on how benefits to participants are negotiated in efficacy trials of biomedical HIV prevention technologies in the developing world.*

The surveys of principal investigators and ethics committee members showed that both sets of stakeholders draw on multiple forms of formal ethical guidance in their decision-making processes. With regard to principal investigators, however, the survey showed significant variation in the ways that standards of prevention and care are conceived, designed and implemented, despite considerable attention given to normative ethics guidance. This was borne out in investigator interviews, in which a spectrum of views was given by informants as to how standards of prevention should be determined. Perceptions ranged from an ethical impetus to include newly validated technologies as soon as feasible to a desire to reduce the prevention package to make it more like "real life", thus enabling subsequent trials to test interventions against basic prevention packages.

Informants were divided as to whether 'equity' meant people having access to the same basic goods within a trial and in the community outside it, or whether 'equity' was about equal access for goods for people participating in trials regardless of where

the trials occur. These competing concepts of social justice are discussed in Pt 3 Chapter 3 *Ethical considerations in determining standard of prevention packages for HIV prevention trials*.

Survey data showed that the ARV access movement has had a decisive impact on the care made available to both seroconverters from trials and, to a lesser extent, volunteers screened out due to pre-existing HIV infection. The impact of broader access to ARV was the key change over time discussed in the interviews, and it was universally welcomed. Investigators permanently based in the countries in which they conducted research tended to be more confident of their ARV access linkages and mechanisms than those who were present in the host country for the duration of the trial only and were reliant upon partners to implement access.

As discussed in Pt 2 Chapter 3, *Ethics of medical care and clinical research* some investigators perceived a stronger obligation to ensure access to ARV for the 'screened out' than they did to people who seroconverted during trial due to the likely more acute medical need of those who discover their HIV infection when enrolling in a trial compared with those who recently seroconverted.

Investigators generally did not report major issues with sponsor policies limiting the way that budgets could be spent on ancillary care and infrastructure in the surveys (particularly those who had conducted recent trials), but containing cost was the major issue raised when the question of adding new interventions to the standard of prevention was discussed. In interviews with those who conducted trials in the early 2000s, informants reported major issues with sponsor policies precluding activities

that investigators deemed warranted particularly with regard to open access to protocols and insurance funds to cover trial-related injury.

Aim 2. *To re-consider the debates about obligations to trial participants in the light of the positive trial results (what are the ethical issues in HIV prevention research in the age of partially effective HIV prevention modalities?).*

There are two main issues here: How partial efficacy affects the obligation for post-trial access, and how the partial efficacy of a particular intervention should affect the design subsequent trials.

As discussed in Pt 2 Chapter 5, *Mind the gap,* principle investigators' obligation to provide post-trial access is limited by their capacity to do so, and the responsibility is shared with other actors including sponsors, government bodies and regulators. Problems with post-trial access evidently occur when not all parties agree whether or not a new intervention should be made available for a given population at a particular time. Interventions that show modest efficacy and are deemed to require confirmatory trials are inherently problematic: participants have a reasonable expectation of getting access, but regulators and governments may be conflicted over potential political consequences of allowing access to a modestly effect product that might have unknown social impacts and that might later be deemed not cost effective in a particular epidemic. Thus the role of the investigator as advocate is an important one.

How newly validated interventions should be incorporated into the design of new trials is discussed in Pt 3 Chapter 3, *Ethical considerations in determining standard of prevention packages for HIV prevention trials, Pt 3* Chapter 2, *How good is 'good enough'* and Pt 3 Chapter 4, *It's time*. These chapters explore the evidentiary,

normative and regulatory bases for determining when a new intervention can be considered 'validated' and argue that there is a particularly compelling case for ensuring both that people at the highest risk of HIV receive optimised prevention packages, and that ongoing HIV prevention research into more user-friendly products is facilitated. The conclusion reached in Pt 3 Chapter 4, *It's time* is that PrEP should become not the standard of prevention but a comparator, so that new experimental interventions that might offer similar biological efficacy to PrEP but have other properties such as being longer acting and hence less adherence-dependent can be measured against an active comparator.

Aim 3. *To understand how principal investigators and ethics committees navigate this territory, and how experience in conducting HIV prevention trials shapes views on how they should be conducted in the future***.**

As discussed in Pt 2 Chapter 4 *Standard of prevention in the real world* there was no consensus as to how principal investigators viewed the way forward in designing HIV prevention trials with active comparators or newly validated interventions added to the standard of prevention. Threads of scientific and ethical argumentation together were used to justify responses. As discussed in Pt 3 Chapter 3 *Ethical considerations in determining standard of prevention packages for HIV prevention trials*, the HPTN guidance validates the use of an effective, but not necessarily optimal, prevention package. Those taking a cautious perspective toward change tended to argue that it would be paradoxical to insist on optimal prevention in trials, as it would slow the speed and increase the cost of research and give trial participants access to a higher level of prevention services than those from the same communities who did not participate. Others saw optimal packages as being of scientific value, in that an

intervention tested against an optimal background is shown to work over and above and above that background, hence offering a genuine advance. In addition, optimal packages could effectively pilot the scale-up of new interventions in a local setting.

There is a broad consensus that for all HIV prevention trials, all study participants should receive a standard HIV prevention package including male and female condoms, STI treatment, and behaviour change communication, as well as education and referral for VMMC in the instance of heterosexual men who are at particular risk of HIV exposure (though in practice this depends on national guidelines, and in at least one major trial did not occur). However, there is a lack of consensus regarding whether PrEP should be part of the standard of prevention package in HIV prevention trials and whether it could be used as a comparator arm. Decisions by country regulatory authorities are not the only factors in making this determination.

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Aim 4. *To explore the factors that affect how and when positive research findings are implemented.*

Positive research findings on three different biomedical HIV prevention modalities were implemented to some degree during this study – medical male circumcision (MMC) in countries with generalised epidemics, oral tenofovir/emtricitabine as PrEP in the United States and earlier ARV treatment for its preventative benefit in various countries**.**

As discussed in Pt 3 Chapter 3, *Ethical considerations in determining standard of prevention packages for HIV prevention trials,* voluntary MMC was added to the standard of prevention in the Phambili vaccine trial following the release of trial data, well before it was incorporated into either World Health Organisation or national guidelines. Subsequent trials that enrolled HIV negative men from areas with generalised epidemics, however, have not necessarily followed suit. The Partners PrEP study had a detailed protocol concerned with providing information and facilitating access to services, but as discussed in Pt 2 Chapter 4, *Standard of prevention in the real world* access depended on government programs, and this happened faster in Kenya than in Uganda. The TDF-2 trial provided information on medical male circumcision once the Botswana government made its recommendation in favour of the practice. HPTN 052 did not provide any systematic information or referral regarding male circumcision at all.

The United States' Food and Drug Administration's approval of oral tenofovir/emtricitabine PrEP is discussed in Pt 2 Chapter 4, *Standard of prevention in the real world,* Pt 3 Chapter 3 *Ethical considerations in determining standard of prevention packages for HIV prevention trials,* Pt 3 Chapter 1 *Ethics of ARV-based prevention* and Part 3 Chapter 4, *It's time*. Several 'demonstration sites' have been set up in the US to both provide PrEP and to monitor its use in terms of efficacy, adherence, toxicities and impact on HIV risk.

The other countries that participated in the iPrEx and Partners PrEP trials, upon which the FDA approvals was based, have made no move to approve PrEP, though short-term access programs have been put in place, as detailed in *Mind the gap* and

demonstration sites have commenced in Kenya and Uganda, with further sites planned in Brazil, Kenya, Nigeria and South Africa (AVAC Report 2012). This raises a set of compelling questions about appropriate technology, the commitment to transform successful research into programmatic interventions in the communities that participated in that research and evidentiary standards. To complicate matters, following the success of iPrEX, Partners PrEP and TDF-2, two subsequent trials featuring PrEP in African women have since failed due to very low adherence, giving rise to speculation that a daily preventative pill regimen may be inappropriate for at-risk some communities or populations.

Treatment-as-prevention has been implemented in the US, in that the federal ARV guidelines have changed to recommend treatment upon diagnosis of HIV infection (Panel on Antiretroviral Guidelines for Adults and Adolescents. 2012). In Zambia, the HIV positive partner in a serodiscordant relationship can access ARV irrespective of CD4 count, and Rwanda and Mozambique are moving towards this. In Britain and Europe, guidelines promote 'considering' ARV irrespective of CD4. China has an official treatment-as-prevention strategy for sero-discordant couples. Elsewhere, a range of countries including Australia[4] promote ARV access at CD4 counts between 350 and 500 (WHO 2012).

Aim 5. *To ask whether there are ethical issues that arise from the empirical research that are not present in the current normative literature.*

One of the key findings of this study, discussed in Pt 3 Chapter 1, *Ethics of medical care and clinical research*, was that that the principal investigators expressed

[4] There are current advocacy efforts aimed at removing any CD4 limit to ARV access in Australia.

considerable identification with the idea of a therapeutic obligation to trial participants – or more broadly, to the communities that facilitated the trial, including individuals who volunteered but were ineligible due to pre-existing HIV infection. The identification of the 'screened out' is a significant case in point, as the perceived obligation to this group is built on doctor-like moral premise that care is owed to those who most need it, rather than stratifying obligations by the depth of the researcher/participant relationship.

For researchers establishing projects in host countries, negotiating the ways that the research site can support existing infrastructure and provide health services in a way that complements rather than replicates local service provision was central to their understanding of their work. For researchers who lived and worked in communities in which they conducted research, HIV prevention and care were part of a continuum rather than disparate activities. For both, the 'therapeutic orientation' in HIV prevention trials appeared indivisible from competent research practice, which challenges the school of bioethics that seeks to further distinguish the activities and goals of research from those of clinical care (e.g. Miller and Brody 2003; Miller and Joffe 2011). Provision of routine primary care in resource-limited setting can ultimately save lives, in addition to the instrumental value of earning the trust that is essential to run such trials.

While researchers were clear that answering the research question remained paramount, the process of conducting a large-scale HIV prevention trial involves complex negotiation with communities and existing health services and ultimately

impacts on the health status of the communities involved and on the surrounding health infrastructure.

These findings are consistent with the concept of clinical research in lower income countries operating as a health intervention that delivers health goods for participants rather than merely as an experiment that produces outcomes in terms of knowledge.

What does this thesis add?

This thesis contributes to the existing empirical on standards of care in HIV prevention trials in the papers Pt 2 Chapter 3, *Ethics of medical care and clinical research,* Pt 2 Chapter 4 *Standard of prevention in the real world,* and Pt 2 Chapter 5 *Mind the gap.* The first two papers provide qualitative data on how principal investigators report making key decisions about ethically sensitive standard of prevention and care issues, with qualitative data on ancillary care considered in the light of different models proposed in existing ethics literature. *Mind the gap* is the first comprehensive account of post-trial access to successful products in the context of HIV prevention, and it highlights what experience proved to be the most effective process for ensuring access to as-yet unapproved products. This is likely to be useful for researchers planning HIV prevention trial who seek to minimise the access problems that other researchers have experienced, as documented in this paper.

This thesis also makes a conceptual, and normative, contribution to the literature. Pt 3 Chapter 1, *Ethics of ARV-based prevention* argues that not only is ARV-based prevention justified in terms of both individual and public health ethical frameworks, but that each has specific validity in different circumstances, and addresses particular

moral claims of individuals and community. Accordingly, each strategy has a place – PrEP for HIV negative people at very high risk of HIV acquisition who are inadequately served by exiting technologies, and treatment as prevention for the sexual partners (whether regular or casual) of HIV positive people.

Pt 3 Chapter 2, *How good is good enough,* provides a critical analysis of the evidentiary regimes that determine drug licensure. It also criticises Freedman's definition of clinical equipoise on the basis that it is an evidence-free social standard prone to manipulation in instances where the experts have conflicts of interest. This analysis has already been used to support the activist group Warning, which seeks to close the placebo arm in the French trial Ipergay, which tests intermittent PrEP in gay men (Olivier Jablonski, personal email communication 8 November 2012).

Finally, Pt 3 Chapter 4 *It's time* makes a clear and carefully nuanced argument that given the both the acknowledged difficulties of PrEP adherence and its high biological efficacy, that PrEP should be the comparator for testing promising new experimental interventions. This would both enable further studies of the factor that affect PrEP adherence and how they may be improved and establish whether or not other experimental interventions offer a real improvement in terms of outcomes.

Clinical trials ought not to be the primary means of delivering health care and prevention justice in countries with endemic HIV. Trials that involve hundreds or thousands of people are however major social enterprises that affect the communities in which they are situated, as well as the participants themselves. While the primary purpose of a trial is to answer a research question, the impact of a trial goes beyond

that – it can increase the research literacy and skill base of the community and strengthen health care infrastructure, for example, and well as directly providing services.

Surprising as it is that two trials have shown no additive effect from PrEP (the VOICE and Fem-PrEP trials where adherence rate were so low that the experimental intervention was futile), it is in some respects the adherence problem associated with PrEP that makes it a good comparator. It is fair to test a promising long-acting intervention of unknown efficacy against one that has high efficacy, but depends entirely upon excellent adherence for effectiveness.

We need to know what works to prevent HIV acquisition and how to maximise the uptake of effective interventions. To continue to test new interventions against placebo at a time when there are imperfect but efficacious interventions like PrEP available exploits the vulnerability of trial populations for the future benefit of others.

Depriving the people at highest risk of HIV acquisition of proven effective prevention options is not the way to obtain prevention justice.

Complete reference list

References

Abdool Karim, Q., S. S. Abdool Karim, J. A. Frohlich, et al. 2010. Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* 329 (5996):1168-1174.

Abdool Karim S.S. and Q. Abdool Karim. 2011 Antiretroviral Prophylaxis: a Defining Moment in HIV control. *Lancet* 378: e23-e25

ACT-UP New York. 2000. *Reports on the Durban International AIDS Conference.* Available at: http://www.actupny.org/reports/durban-who.html [Accessed 3 March 2010]

ACT-UP Paris, 2008. 'ACT-UP-Paris and treatment activism', http://www.actupparis.org/article3482.html [Accessed 12 September 2009].

K. Alcorn. 2005. Thai Tenofovir Trial Runs into Trouble After Ethics Protests from Drug Users. *Aidsmap* 2005.Available at: http://www.aidsmap.com/en/news/AF0B8B91-A54B-4632-9736-03F66FE37CF5.asp Accessed 14 January 2010.

Anderson, P.L., D. V. Glidden, A. Liu, et al. 2012. Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men. *Science Translational Medicine* 4 (151):151ra125

Anderson P, Liu A, Buchbinder S, et al; the iPrEx Study Team. 2012. Intracellular tenofovir-DP concentrations associated with PrEP efficacy in MSM from iPrEx.

Presented at: 19th Conference on Retroviruses and Opportunistic Infections; March 2012; Seattle, Washington

Anderson, R. M. and G. P. Garnett. 1996. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *The Lancet* **348** (9033): 1010-1013.

Angell, Marcia. 1997. The ethics of clinical research in the third world. *The New England Journal of Medicine* 337 (12): 847-849.

Antiretroviral Therapy Cohort Collaboration. 2008. Life Expectancy of Individuals on Combination Antiretroviral Therapy in High-Income Countries: A Collaborative Analysis of 14 Cohort Studies. *The Lancet* 372: 93-299

Ashcroft, R. 1999. Equipoise, Knowledge and Ethics in Clinical Research and Practice. *Bioethics* 13(3-4): 314-326.

Auvert, B., D. Taljaard, E. Lagarde, Joëlle Sobngwi-Tambekou, Rémi Sitta, and Adrian Puren. 2005. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLoS Med* 2 (11):e298.

AVAC (AIDS Vaccine Advocacy Coalition). 2005. Will a pill a day prevent HIV? [Report on the internet], Available at: http://www.avac.org/ht/a/GetDocumentAction/i/3116 [Accessed 13 January 2010]

AVAC. 2010. Frequently Asked Questions about PrEP and the iPrEx Trial.

AVAC, November 23, 2010: p 6-7. Accessed 28 January 2011. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/31348

AVAC. 2011. Frequently asked questions about FEM-PrEP. Accessed 11 May 2011. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/33632

AVAC. ARV-Based Prevention Options Timeline Available at: http://www.avac.org/ht/a/GetDocumentAction/i/46212 Accessed 5 March 2013.

AVAC Report 2012. Achieving the end-one year and counting. www.avac.org/report2012 Accessed 11 March 2012.

AVAC PrEP Research to Rollout: A schematic road map. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/49134

Baeten, J. M., D. Donnell, P. Ndase, et al. 2012. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine* 367 (5):399-410.

Bailey, R.C, S Moses, C.B Parker, et al. 2007. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 369:643 - 656.

Barr, D., J. J. Amon, M. Clayton. 2011. Articulating a Rights-Based Approach to HIV Treatment and Prevention Interventions. *Current HIV Research* 9 (6):396-404.

Bass, E. 2004. IIb or nor IIb: AIDS vaccine trial sponsors weigh the merits of intermediate-size efficacy trials. *IAVI Report* 8(1) Available at: http://www.iavireport.org/Back-Issues/Pages/IAVI-Report-08(1)-IIbornotIIb.aspx

Baume P. A question of balance: report on the future of drug evaluation in Australia. Canberra: Australian Government Publishing Service, 1991.

Bayer, R. 1989. Isolating the infected: the politics of control . *Private Acts, Social Consequences.* New York, The Free Press**:** 169-206.

Beauchamp, T., and J. Childress. 1994. *Principles of biomedical ethics*. 4th ed. New York, Oxford: Oxford University Press. Original edition, 1979.

Beecher, H. K. 1966. Ethics and Clinical Research. *New England Journal of Medicine* 274 (24):1354-1360.

Beloqui, J. 2008. International Rectal Microbicides Advocates: listserv communication. Available at: http://critpath.org/pipermail/rectalmicro_critpath.org/2008-November/000564.html [Accessed 13 January 2010]

Belsky, L., and H. S Richardson. 2004. Medical researchers' ancillary clinical care responsibilities. *British Medical Journal* 328 (7454):1494-1496.

Benatar, S. R. 2001. Justice and Medical Research: A Global Perspective. *Bioethics* 15 (4):333-340.

Bhaskaran, K. 2008. Changes In The Risk Of Death After HIV Seroconversion Compared with Mortality in the General Population. *Journal of the American Medical Association*, 300: 51-59

Bloom B. R. 1998. The highest attainable standard: Ethical issues in AIDS vaccines. *Science* 279: 186-188.

Bright P.L. and R.M. Nelson. 2012. A capacity-based approach for addressing ancillary care needs: implications for research in resource limited settings. *J Med Ethics* 38(11):672-6.

Buchbinder, S. P., D.V. Mehrotra, A. Duerr, et al. 2008. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *The Lancet* 372 (9653):1881-1893.

Cardo, D. M., D. H. Culver, C. A. Ciesielski, et al. 1997. A Case–Control Study of HIV Seroconversion in Health Care Workers after Percutaneous Exposure. *New England Journal of Medicine* 337 (21):1485-1490.

Carrese,J.A., J. Sugarman. 2006. The inescapable relevance of bioethics for the practicing clinician. *Chest*130(6):1864-72.

Centers for Disease Control. 1999. Case-Control Study of HIV seroconversion in health-care workers after percutaneous exposure to HIV infected blood- France, United Kingdom, and United States, January 1988-August 1994, *Morbidity and Mortality Weekly Report* 44:929-33

Centers for Disease Control. 2010. Pre-Exposure Prophylaxis (PrEP) for HIV Prevention: Promoting Safe and Effective Use in the United States. Press statement. November 23, 2010.

Available at:

http://www.cdc.gov/nchhstp/newsroom/PrEPforHIVFactSheet.html

Accessed January 23, 2010.

Centers for Disease Control. 2011. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. *Morbidity and Mortality Weekly Report* 60(03): 65-68.

Centers for Disease Control. (CDC). 2012. CDC Issues Interim Guidance on Use of Medication to Prevent HIV Infection among Heterosexually Active Adults. (News release)August 9 2012. Atlanta, GA: CDC. [Accessed October 14 2012]

Available at: http://www.cdc.gov/nchhstp/newsroom/2012/PrEP-HeterosexualGuidance-PressRelease.html

Centre for the AIDS Programme of Research in South Africa (CAPRISA). CAPRISA 008 MCC Correspondence: Sequence of Events; Q. Abdool Karim, S.S Abdool Karim & L. Mansoor. Letter to Dr Portia Nkambule, Medicines Control Council. 22 March 2012.

Chua, A. N. Ford & D. Wilson, et al. 2005. The Tenofovir Pre-Exposure Prophylaxis Trial in Thailand: Researchers Should Show More Openness in Their Engagement with the Community, *PLoS Med* 2: 1044-1045

Cohen, M. S., Y. Q. Chen, M. McCauley, et al. 2011. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine* 365 (6):493-505.

Cohen, M. S., M. McCauley, and J. Sugarman. 2012. Establishing HIV treatment as prevention in the HIV Prevention Trials Network 052 randomized trial: an ethical odyssey. *Clinical Trials* 9(3):340-34

Connor, E. M., R. S. Sperling, R. Gelber, et al. 1994. Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment. *New England Journal of Medicine* 331 (18):1173-1180.

CONRAD.2010. FDA and CONRAD Chart U.S. Regulatory Path for 1% Tenofovir Gel for HIV Prevention: FDA has granted Fast Track approval designation for 1% tenofovir gel. Press statement. 25 October, 2010. Available at: http://www.natap.org/2010/newsUpdates/110110_01.htm Accessed January 23, 2010.

CONRAD. FDA and CONRAD Chart U.S. Regulatory Path for 1% Tenofovir Gel for HIV Prevention: Collaborative meeting held with key stakeholders. 2010. Available at: http://www.conrad.org/media/news/88_CONRAD%20FDA%20Meeting%20Release%2020%20Final.doc. [Accessed 6 March 2013].

Cooper, E.R. M. Charurat, L. Mofenson, et al. 2002. Combination Antiretroviral Strategies for the Treatment of Pregnant HIV-1-Infected Women and

Prevention of Perinatal HIV-1 Transmission. *Journal of Acquired Immune Deficiency Syndromes* 2002; 29: 484-494

Diarra, A. 2001. Making a Public-Private Partnership Work - An Insider's View. Bulletin of the World Health Organization 79: 795-796

De Zulueta, P. 2001. Randomised Placebo-Controlled Trials and HIV-Infected Pregnant Women in Developing Countries: Ethical Imperialism or Unethical Exploitation? *Bioethics* 15 (4):289-311.

de Zoysa, I., Elias, C. J., & Bentley, M. E. 1998. Ethical challenges in efficacy trials of vaginal microbicides for HIV prevention. *American Journal of Public Health* 88(4): 571-5

Council for International Organizations of Medical Sciences (CIOMS). 2002. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available at: http://www.cioms.ch/publications/layout_guide2002.pdf Accessed 23 March 2013.

Council of Europe's Steering Committee on Bioethics (CDBI). Available at: http://www.coe.int/t/dg3/healthbioethic/cdbi/default_en.asp Accessed 23 March 2013.

Edgar, H and Rothman, D. 1990. New Rules for New Drugs: The Challenge of AIDS to the Regulatory Process. *The Milbank Quarterly* 68, Suppl 1: 111-142.

Essack, Z., C. Slack, J. Koen, and G. Gray. 2010. HIV prevention responsibilities in HIV vaccine trials: Complexities facing South African researchers. *South African Medical Journal* 100 (1):45-48.

Zaynab E., J. Koen, N. Barsdorf, et al. 2010. Stakeholder perspectives on ethical challenges in HIV vaccine trials in South Africa. *Developing World Bioethics* 10 (1):11-21

European Group on Ethics in Science and New Technologies (EGE). Available at: European Group on Ethics in Science and New Technologies Accessed 23 March 2013.

Fawkes, J. The Cambodian PrEP Trial: The Sex Workers' Perspective. [Powerpoint presentation]. *The 2nd symposium on microbicides and HIV biomedical prevention*, Sydney, July 14, 2008.

Feldblum, P.J., A. Adeiga, R. Bakare, et al. 2008. SAVVY Vaginal Gel (C31G) for Prevention of HIV Infection: A Randomized Controlled Trial in Nigeria. *PLoS ONE* 3: e1474

Fitzgerald, D.W., J.W. Pape, J.N. Wasserheit, G.W. Counts, and L. Corey. 2003. Provision of treatment in HIV-1 vaccine trials in developing countries. *The Lancet* 362: 993–994.

Fleming, T. 2013. Non-inferiority clinical trials. Some key consideration in PrEP and microbicide studies. Presentation at the meeting on the Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues, Washington, January 7, 2013 http://www.hivforum.org/storage/hivforum/documents/FutureofPrEP/session_2_fleming.pdf [Accessed February 1, 2013]

Flynn, N. M., D. N. Forthal, C. D. Harro, et al. 2005. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *The Journal of infectious diseases* 191 (5):654-65.

Food and Drug Administration. (FDA). 2012. FDA Approves First Drug for Reducing the Risk of Sexually Acquired HIV Infection. (News release) July 16 2012. Silver Spring, MD: FDA. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm [Accessed September 10, 2012]

Food and Drug Administration. (FDA). 2012 Meeting Materials Antiviral Advisory Committee. May 11 2012 meeting of the Antiviral Drug Advisory Committee Questions to the committee available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM305774.pdf [Accessed 6 Oct 2012]

Transcript of meeting available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM311519.pdf [Accessed 6 Oct 2012]

All meeting materials available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm295937.htm [Accessed 6 Oct 2012]

Forbes, A. S Mudaliar. 2009. Preventing Prevention Trial Failures: A Case Study and Lessons Learned for Future Trials from the 2004 Tenofovir Trial in Cambodia Washington: Global Campaign for Microbicides.

Forbes A., Moving Towards Assured Access to Treatment in Microbicide Trials. 2006. *PLoS Medicine* 3 (7), e153: 980-983

Fried C. 1974. *Medical experimentation: personal integrity and social policy*. Amsterdam: North-Holland Publishing.

Freedman, B. 1987. Equipoise and the Ethics of Clinical Research. *New England Journal of Medicine* 317(3): 141-145.

Geffen, N. What Happened in Durban? A South African Perspective. Gay Men's Health Crisis. September/October 2000.[Report on the Internet] Available at The Body http://www.thebody.com/content/art13213.html [Accessed 21 February 2010]

Gibbs, J.. Verdict on a virus. IRMA Rectal Microbicides Advocacy blog. http://irma-rectalmicrobicides.blogspot.com.au/2011/11/pros-and-cons-of-treatment-as.html Accessed July 31 2012

Gilbert, P.B. J.O. Berger, D. Stablein, et al. 2011. Statistical Interpretation of the RV144 HIV Vaccine Efficacy Trial in Thailand: A Case Study for Statistical Issues in Efficacy Trials. *Journal of Infectious Diseases* 203: 969-975

Global Campaign for Microbicides. Statement on FDA Regulatory Pathway for 1% Tenofovir Available at: http://www.globalcampaign.org/clientfiles/CONRAD%20FDA%20TFV%20GCM%20Statement.doc. Accessed 1 December 2010.

Global Network of People Living with HIV. About the Global Criminalisation Scan. Available at: http://www.gnpplus.net/criminalisation. Accessed July 31, 2012.

Grant, R. M. 2010. Antiretroviral Agents Used by HIV-Uninfected Persons for Prevention: Pre- and Postexposure Prophylaxis. *Clinical Infectious Diseases* 50(Supplement 3): S96-S101.

Grant, R. M., J. R. Lama, P. L. Anderson, et al. 2010. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *New England Journal of Medicine* 363 (27):2587-2599.

Gray, G., S. Buchbinder and A. Duerr. 2010. Overview of STEP and Phambili trial results: two phase IIb test-of-concept studies investigating the efficacy of MRK adenovirus type 5 gag/pol/nef subtype B HIV vaccine. Current Opinion in HIV AIDS. 5(5):357-61.

Gray, R.H., G. Kigozi, D. Serwadda, et al. 2007. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. The *Lancet* 369:657 - 666.

Haire B.G. Because we can: clashes of perspective over obligation in the failed PrEP trials. *Developing World Bioethics* 2011;11: 63-74

Haire, B. 2011. Treatment-as-Prevention Needs to Be Considered in the Just Allocation of HIV Drugs. *The American Journal of Bioethics* 11 (12):48-50.

Haire, B., J. Kaldor, and C. F. C. Jordens. 2012. How Good Is "Good Enough"? The Case for Varying Standards of Evidence According to Need for New Interventions in HIV Prevention. *The American Journal of Bioethics* 12 (6):21-30.

Hankins, C.A., M.R.Dybul. 2013.The promise of pre-exposure prophylaxis with antiretroviral drugs to prevent HIV transmission: a review. *Current Opinion in HIV/AIDS* 8(1):50-8.

Hankins, C., R. Macklin, N. Michael, D. Stablein and participants. Meeting Report. Recommendations for the Future Utility of the RV144 Vaccines to the Thai Ministry of Health. March 16-18, 2010.

Heise, L.L., C.Watts, A. Foss, et al. 2011. Apples and oranges? Interpreting success in HIV prevention trials. *Contraception* 83 (1):10-15..

Heise,L., K. Shapiro and K. West Slevin. 2008. Mapping the Standards of Care at Microbicide Clinical Trial Sites. Washington DC: Global Campaign for Microbicides.

Holt, M., D.A. Murphy , D. Callander et al. Willingness to use HIV pre-exposure prophylaxis and the likelihood of decreased condom use are both associated with unprotected anal intercourse and the perceived likelihood of becoming HIV-positive among Australian gay and bisexual men. *Sexually Transmitted Infections*, 2012; 88, 258-263

Hirnschall, G., and B. Schwartländer. 2011. Treatment 2.0: catalysing the next phase of scale-up. *The Lancet* 378 (9787):209-211.

HIV Vaccine Trials Network (HVTN) 505 Study. *HVTN 505: Expansion in Response to an Evolving Field.* Seattle, WA: HVTN Available at: http://hvtnews.wordpress.com/2011/09/13/hvtn-505-expansion-in-response-to-an-evolving-field/ [Accessed October 31 2012]

Ipergay Study. http://www.ipergay.fr

International AIDS Vaccine Initiative. (IAVI). Understanding Vaccine Licensure. What factors do regulatory bodies consider before licensing a vaccine for public use? Vax 2009; 7 (12).

Available at: http://www.vaxreport.org/Back-Issues/Pages/UnderstandingVaccineLicensure.aspx

International Conference on Harmonization Good Clinical practice (ICH-GCP). 1996. Available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf

Accessed 23 March 2013.

International Planned Parenthood Federation, Global Network of People Living with HIV/AIDS, International Community of Women Living with HIV/AIDS. HIV - Verdict on a Virus: Public Health, Human Rights and Criminal Law. 2008. Available at: http://www.gnpplus.net/images/stories/2008_verdict_on_a_virus.pdf. Accessed July 31, 2012

International Rectal Microbicide Advocates. 2010. *From Promise to Product: Advancing Rectal Microbicide Research and Advocacy*. Pittsburgh, IRMA.

Jaffe, H. W. and T. Hope. 2010. Treating for the Common Good: A Proposed Ethical Framework. *Public Health Ethics* 3(3): 193-198.

James, J.S. Access to Treatment Worldwide: From Talk to Action at Durban *Aids Treatment News* 2000. Issue #347, July 28. Available at: http://www.aegis.org/pubs/atn/2000/ATN34703.html [Accessed 21 February 2010]

Jansen, L. A. 2005. A Closer Look at the Bad Deal Trial: Beyond Clinical Equipoise. *The Hastings Center Report* **35**(5): 29-36.

Accessed 2 February 2013

Jintarkanon, S., S. Nakapiew, and N. Tienudom, et al. 2005. Unethical Clinical Trials in Thailand: A Community Response (letter). *The Lancet* 365: 1617-1618

Joffe, S., and F. G. Miller. 2012. Equipoise: asking the right questions for clinical trial design. *Nature Reviews Clinical Oncololgy* 9 (4):230-235.

Jonsen A.R. Bentham in a box: Technology and healthcare allocation. *L Med &*

Healthcare 1986; **14**:172- 174

Kaldor, J.M. and D.P. Wilson. How low can you go: the impact of a modestly effective HIV vaccine compared with male circumcision. *AIDS* 2010; 24: 2573-2578 10.1097/QAD.0b013e32833ead96.

Kilmarx, P. H.,G. Ramjee, D. Kitayaporn, and P.Kunasol 2001.Protection of human subjects' rights in HIV preventive clinical trials in Africa and Asia: Experiences and recommendations. AIDS15(supplement 4): S1–S7

Knox, Richard and Michaeleen Doucleff. 2012. Clinton Reveals Blueprint For An 'AIDS-Free Generation'. *Shots: Health News*, http://www.npr.org/blogs/health/2012/11/29/166154269/clinton-reveals-blueprint-for-an-aids-free-generation.

Kopelman, L. 1986. Consent and randomised clinical trials: are there moral or design problems? *Journal of Medicine and Philosophy* 11: 317-345.

J.M. Lange. 2005. We Must Not Let Protestors Derail Trials of Pre-Exposure Prophylaxis for HIV. *PLoS Medicine* 2: 833-834. Available at: http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.0020248

Lemmens, T., and P. B. Miller. 2002. Avoiding a Jekyll-And-Hyde Approach to the Ethics of Clinical Research and Practice. *The American Journal of Bioethics* 2 (2):14-17.

Levine, R. J. 1999. The Need to Revise the Declaration of Helsinki. *New England Journal of Medicine* 341 (7):531-534.

Lissouba, P., D. Taljaard, D. Rech, et al. A Model for the Roll-Out of Comprehensive Adult Male Circumcision Services in African Low-Income Settings of High

HIV Incidence: The ANRS 12126 Bophelo Pele Project. *PLoS Medicine* 2010; 7: e1000309.

Lo, B., N. Padian and M. Barnes. 2007. The obligation to provide antiretroviral treatment in HIV prevention trials. *AIDS* 21: 1229-1231.

Loff, B., J. Black. 2000. The Declaration of Helsinki and Research in Vulnerable Population. *Medical Journal of Australia* 172: 292-295

Loff, B. C. Jenkins & M. Ditmore et al. 2005. Letter to the editor (untitled), *The Lancet* 365: 1618-1619

London, A. J. 2000. The Ambiguity and the Exigency: Clarifying 'Standard of Care' Arguments in International Research. *Journal of Medicine and Philosophy* 25 (4):379-397.

London, A., and Zollman, K. 2010. Research at the Auction Block: Problems for the Fair Benefits Approach to International Research. *The Hastings Center Report*, 40(4): 34-45.

Lurie, P., and S. M. Wolfe. 1997. Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries. *New England Journal of Medicine* 337 (12):853-856.

McCormack, S. Perspectives of a clinical researcher at the stage of grant writing. Standards of care in Future Microbicides Research Symposium. Presentation at the M2012 symposium. Microbicide 2012, Sydney, Australia. April 15th to 19th, 2012.

McGrory, E., A. Irvin, L. Heise. 2009.*Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site. Washington, DC: Global Campaign for Microbicides at PATH; Available at:*

www.globalcampaign.org/clientfiles/Cameroon.pdf. *Accessed: 8 January 2011*.

McGrory E, S. Philpot, C. Hankins, L. Paxton, L. Heise. 2010. *Standards of Prevention in HIV Prevention Trials: Consultation Report and Recommendations.* Washington DC, Global Campaign for Microbicides at PATH.

Macklin, R. 1999. *Against relativism : cultural diversity and the search for ethical universals in medicine*. New York: Oxford University Press.

Macklin, R. 2001. After Helsinki: Unresolved Issues in International Research. *Kennedy Institute of Ethics Journal* 11 (1):17-36.

Macklin, R. 2004. *Double standards in medical research in developing countries.* Cambridge; New York: Cambridge University Press.

Macklin, R. 2004. Striving For a Single Standard in *Double Standards in Medical Research in Developing Countries* Cambridge; New York Cambridge University Press, pp101-102.

Macklin, Ruth. 2006. Changing the Presumption: Providing ART to Vaccine Research Participants. *The American Journal of Bioethics* 6 (1):1 - 5.

Macklin, Ruth. 2008. Standard of care: an evolution in ethical thinking. *The Lancet* 372 (9635):284-285.

Macklin, R., 2011. Ethical challenges in HIV microbicide research: What protections do women need? *International Journal of Feminist Approaches to Bioethics* 2011; 4: 124-142, 128.

McNeill, D.G. 2000. Agencies Urge Use of Affordable Drug for H.I.V. in Africa. *New York Times* (online.) 6 April. Available at

http://www.nytimes.com/2000/04/06/world/agencies-urge-use-of-affordable-drug-for-hiv-in-africa.html?pagewanted=1 [Accessed 13 January 2010]

Mann, J. M. 1997. Medicine and Public Health, Ethics and Human Rights. *The Hastings Center Report* 27 (3):6-13.

May M., M. Gompels and C. Sabin. 2012. *Life expectancy of HIV-1-positive individuals approaches normal, conditional on response to antiretroviral therapy: UK collaborative HIV cohort study*. Eleventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract O133, 2012.

Mayer, K. 2013. Future of PrEP and Microbicide Research: Setting the Stage. Presentation at the meeting on the Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues, Washington, January 7, 2013. Available at: http://www.hivforum.org/storage/hivforum/documents/FutureofPrEP/session_1_mayer.pdf [accessed February 2, 2013]

Marrazzo, J., G Ramjee, G Nair, et al. 2013.Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine or vaginal tenofovir gel in the VOICE study (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 26LB, 2013.

Medical Research Council (MRC). 2003.Policy on antiretroviral therapy (ART). Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002455 Accessed 23 March 2013.

Medical Research Council (MRC). 2004. Research Involving Human Participants in Developing Societies. Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002461

Accessed 23 March 2013.

Merkatz, R. S. White Junod. 1994. The historical background of changes in FDA policy on the study and evaluation of drugs in women. *Academic Medicine* 69(9): 703-7.

Merritt M &C. Grady.2006. Reciprocity and post-trial access for participants in antiretroviral therapy trials. *AIDS*; 20: 1791–1794

Microbicides Trial Network. Protocol. 2010 MTN-003 Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women (VOICE). Version 2. Available at: http://www.mtnstopshiv.org/sites/default/files/attachments/MTN003_FINAL_Version_2.0_31DEC200.pdf Accessed 5 March 2013

Microbicides Trials Network (MTN). Questions and Answers. Decision to Modify Voice: Outcome of November 17 Data and Safety Monitoring Board (DSMB) Review of Voice. November 17, 2011. Available at: http://www.mtnstopshiv.org/node/3908. Access 30 January 2013.

Microbicides Trial Network. MTN Statement on Decision to Discontinue Use of Oral Tenofovir Tablets in VOICE, a Major HIV Prevention Study in Women. September 28, 2011. Pittsburgh, PA: MTN. Available at: ***http://www.mtnstopshiv.org/node/3619*** [Accessed 24 September 2012]

Microbicides Trial Network. MTN Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women. Nov 25, 2011. Pittsburgh, PA: MTN Available at: http://www.mtnstopshiv.org/node/3909[Accessed 24 September 2012]

Microbicide Trials Network. (MTN). 2013. Understanding the results of VOICE. Available at: http://www.mtnstopshiv.org/news/studies/mtn003 Accessed 12 March 2013.

Miller, F. G. and H. Brody. 2003. A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials. *The Hastings Center Report* 33(3): 19-28.

Miller, F.G. and H. Brody. 2003. The Clinician-Investigator: Unavoidable but Manageable Tension. *Kennedy Institute of Ethics Journal* 13 (4):329-346

Miller, F. G., and H. Brody. 2007. Clinical Equipoise and the Incoherence of Research Ethics. *Journal of Medicine and Philosophy* 32 (2):151-165.

Miller, F. G., and S. Joffe. 2011. Equipoise and the Dilemma of Randomized Clinical Trials. *New England Journal of Medicine* 364 (5):476-480.

Miller J and B. Glasner. 2004. The "Inside" and the "Outside": Finding realities in interviews in D. Silverman (ed) *Qualitative Research: Theory, Method and Practice*. London: Sage, 2004: 125-129

Miller, P. B., and C. Weijer. 2006. Fiduciary Obligation in Clinical Research. *The Journal of Law, Medicine & Ethics* 34 (2):424-440.

Miller, P. B., Weijer, C. 2007. Equipoise and the Duty of Care in Clinical Research: A Philosophical Response to Our Critics. *Journal of Medicine and Philosophy* 32(2): 117-133.

Mills, E., S. Singh, J. Singh et al. 2005. Designing Research in Vulnerable Populations: Lessons from the HIV Prevention Trials that Stopped Early. *British Medical Journal*, 331: 1403-1406

E. Mills, B. Rachlis, P. Wu, et al. 2005.Media Reporting of Tenofovir Trials in Cambodia and Cameroon. *BMC International Health and Human Rights* 5 (6).

Millum J. 2011. Post-trial access to antiretrovirals: Who owes what to whom? *Bioethics* 25: 145154

Minister of Health and Others v Treatment Action Campaign and Others (No 1) (CCT9/02) [2002] ZACC 16; 2002 (5) SA 703; 2002 (10) BCLR 1075 (5 July 2002). http://www.saflii.org/za/cases/ZACC/2002/16.html

Moatti, J.P., I. N'Doye & S. M. Hammer et al. 2003. Antiretroviral Treatment for HIV Infection in Developing Countries: An Attainable New Paradigm. *Nature Medicine* 9: 1449-52.

National Bioethics Advisory Commission (NBAC). 2001. Ethical and policy issues in international research: Clinical trials in developing countries. Bethesda, Maryland. Available at: http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf Accessed 23 March 2012.

The National Committee to Review Current Procedures from Approval of New Drugs for Cancer and AIDS (Lasagna Commission) *Final Report* (August 15 1990).

New HIV Vaccine and Microbicides Advocacy Society (NHVMAS). 2012. Research Community Request For Better Process Of Community Engagement, Informed Consent And Standard Of Care in HIV Research in Nigeria. Lagos, Nigeria:NHVMAS. Available at: http://nhvmas-ng.org/website/eventcontent.php?eventid=%20141

Ndebele, P., D. Wassenaar, E. Munalula and F. Masiye. 2012. Improving understanding of clinical trial procedures among low literacy populations: an intervention within a microbicide trial in Malawi. BMC Medical Ethics 13: 29.

New York Department of Health. 1999.Confidence intervals: statistics teaching tools. Available at: http://www.health.state.ny.us/diseases/chronic/confint.htm Accessed 26 April 2011.

Nuffield Council on Bioethics. 2007. *Public health: ethical issues*. Chapter 2 (An Ethical Framework) Available at: http://www.nuffieldbioethics.org/sites/default/files/files/Public%20health%20Chapter%202%20-%20An%20ethical%20framework.pdf Accessed 23 March 2013.

Nuffield Council on Bioethics. 2005. The ethics of research related to healthcare in developing countries: a follow-up discussion paper. Out of print.

Nunn, A., S. McCormack, A. Crook, R. Pool, C. Rutterford and R. Hayes. 2009. Microbicides Development Programme: design of a phase III trial to measure the efficacy of the vaginal microbicide PRO 2000/5 for HIV prevention. *Trials* 10(1): 99

Padian, N.S., A. Buvé, J. Balkus, D., Serwadda, W. Cates Jr. 2008. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. *Lancet.* 372(9638):585-99.

Padian, N.S., A. Straten, G. Ramjee, et al. 2007. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomized controlled trial. *Lancet* 370:251 - 261.

Page-Shafer, K., V. Saphonn, L. P. Sun, et al. 2005. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. *The Lancet* 366 (9495):1499-1503.

Panel on Antiretroviral Guidelines for Adults and Adolescents. 2013. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 11 March 2012.

Pantaleo, G., M. Esteban, B. Jacobs & J. Tartaglia. Poxvirus vector-based HIV vaccines. 2010.*Current Opinion in HIV and AIDS* 5: 391-396 10.1097/COH.0b013e32833d1e87.

Partners PrEP. Protocol Addendum #8, 28 July 2011. Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV -1 Acquisition within HIV-1 Discordant Couples. Version 3.0, 12 October 2007 p 2

Peterson, L., D. Taylor, R. Roddy, et al. 2007. Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial *PLOS Clinical Trials* 2 (5):e27.

Philpott, S., K. West Slevin, K. Shapiro, and L. Heise. 2010. Impact of Donor-imposed Requirements and Restrictions on Standards of Prevention and Access to Care and Treatment in HIV Prevention Trials. *Public Health Ethics* 3 (3):220-228.

Philpott, S., L. Heise, E. McGrory, et al. 2011. The challenge of defining standards of prevention in HIV prevention trials. *Journal of Medical Ethics* 37 (4):244-248.

Powers, M. ‘Theories of justice in the context of research’ in Jeffrey P Kahn, Anna

Mastroianni, Jeremy Sugarman, ed. *Beyond Consent: Seeking Justice in Research*. 1998, Oxford University Press: Ox ford New York. 190.

Poynten, I.M., Jin, F., Mao, L.,et al. 2009. Nonoccupational postexposure prophylaxis, subsequent risk behaviour and HIV incidence in a cohort of Australian homosexual men *AIDS* 23 (9):1119-26.

Press release. Terms of deal to make gel affordable and accessible in Africa following regulatory approval. *Eureka Alert* 2010. Available at: http://www.hst.org.za/news/next-steps-tenofovir-gel-conrad-and-tia-sign-license-agreement [Accessed 5 March, 2013]

Ramjee G, Kamali A, McCormack S. 2010. The last decade of microbicide clinical trials in Africa: from hypothesis to facts. *AIDS* Suppl 4:S40-9.

Rennie S, J. Sugarman and the HPTN Ethics Working Group. 2009. HIV Prevention Trials Network Ethics Guidance for Research, HIV Prevention Trials Network.

Rennie, Stuart, and Jeremy Sugarman. 2010. Developing ethics guidance for HIV prevention research: the HIV Prevention Trials Network approach. *Journal of Medical Ethics* 36 (12):810-815.

Rerks-Ngarm, S., P. Pitisuttithum, S.Nitayaphan, et al. 2009. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *New England Journal of Medicine* 361(23):2209-2220.

Richardson, H. S. 2007. Gradations of Researchers' Obligation to Provide Ancillary Care for HIV/AIDS in Developing Countries. *American Journal of Public Health* 97(11):1956-1961

Rosen, Sydney, and Matthew P. Fox. 2011. Retention in HIV Care between Testing and Treatment in Sub-Saharan Africa: A Systematic Review. *PLoS Medicine* 8(7):e1001056.

RV144 Follow-up Study RV305 Begins in Thailand. November 4 2012. Available at: http://www.hivresearch.org/news.php?NewsID=238 [Accessed 6 March 2013].

Schneider, H., D., Blaauw, L. Gilson, N. Chabikuli, and J. Goudge. 2006. Health Systems and Access to Antiretroviral Drugs for HIV in Southern Africa: Service Delivery and Human Resources Challenges. *Reproductive Health Matters* 14 (27):12-23.

Schouten E.J., A. Jahn, D. Midiani, et al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. *Lancet* 2011; 378: 282–84

Schüklenk, U. 2010. Calling it a day on proceduralism in bioethics? *Bioethics* **24**(9): ii-ii.

Schroeder D. & E. Gefenas. 2011. Realising benefit sharing – The case of post-study obligations. *Bioethics* 26(6): 305-314.

Shapiro, K., and S.R. Benatar. 2005. HIV prevention research and global inequality: steps towards improved standards of care. *Journal of Medical Ethics* 31 (1):39 - 47.

Silverman J., M.R. Decker, N. Saggurti, D. Balaiah, and A. Raj. 2008. Intimate partner violence and HIV infection among married Indian women. *JAMA: The Journal of the American Medical Association* 300 (6):703-710.

Singer, P. A., and S. R. Benatar. 2001. Beyond Helsinki: a vision for global health ethics. *BMJ* 322 (7289):747-748.

Skoler-Karpoff, S., G. Ramjee, K. Ahmed, et al. 2008. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. *The Lancet* 372:1977 - 1987.

Slack, C., M. Stobie, C. Milford, et al. 2005. Provision of HIV treatment in HIV preventive vaccine trials: a developing country perspective. *Social Science and Medicine* 60(6): 1197-1208.

South African Department of Health. Report on the 13th International AIDS Conference, Durban, 9 – 14 July 2000. Summary Report of Major Issues, Conclusions and Recommendations. [Report on the internet.] –section 7.3. Available at: http://www.doh.gov.za/aids/docs/13conf00.html

Stadler J., and E. Saethre. 2010. Blockage and flow: intimate experiences of condoms and microbicides in a South African clinical trial. *Culture, Health & Sexuality: An International Journal for Research, Intervention and Care* 13(1): 31-34.

Strategic Timing of Anti-Retroviral Treatment (START study) (2011) http://www.niaid.nih.gov/volunteer/hivandinfectious/hivstudies/Pages/START Study.aspx.

Steinbrook R. 2006. Compensation for Injured Research Subjects. *New England Journal of Medicine* 354: 1871-73

Strategies for Management of Antiretroviral Therapy Study Group.(SMART Study) (2008). Major Clinical Outcomes in Antiretroviral Therapy (ART)–Naive Participants and in Those Not Receiving ART at Baseline in the SMART Study. *J Inf Diseases* 2008 **197**(8): 1133-1144.

Stone, A. 2009. *Regulatory Issues in Microbicide Development.* World Health Organisation.

Strubb, S. 2010. Medical Ethics and the Rights of People with HIV Under Assault. Poz Blogs, Poz. 2012.

Strubb, S. 2012. Public Health or Slippery Slope? Poz Blogs, Poz. **2012**.

Thigpen, M. C., P. M. Kebaabetswe, L.A. Paxton, et al. 2012. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *New England Journal of Medicine* 367 (5):423-434.

Track C Session summary TUWS02. Implementing Pre-exposure Prophylaxis: Current Progress and Future Challenges. AIDS 2012. Available at: http://rapporteurs.aids2012.org/SummaryView.aspx?summary_id=187 Accessed 6 March 2013.

Treatment Action Campaign (TAC). TAC Briefing on Adult and Adolescent Voluntary Medical Male Circumcision (VMMC). Capetown, South Africa:TAC. Available at:

http://www.tac.org.za/community/node/3190 [Accessed 25 September 2012

Ukpong M.O. 2012 . Perspectives on Community Engagement in Standard of Prevention Package Negotiation for Clinical Trials. Presentation at the M2012 symposium. Microbicide 2012, Sydney, Australia, USA. April 15th to 19th, 2012.

Ukpong, M., and K. Peterson, eds. 2009. *Oral Tenofovir Controversy II: Voices from the Field*. Falomo, Nigeria: New HIV Vaccines and Microbicides Society (NHVMAS).

UNAIDS/WHO. 2007. "Ethical considerations in biomedical HIV prevention trials [monograph on the Internet]." Joint United Nations Programme on HIV/AIDS (UNAIDS).

UNAIDS/World Health Organization (WHO). 2007.UNAIDS/07.28E/JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS/WHO Guidance Document. Geneva: UNAIDS and World Health Organization. Available at:http://data.unaids.org/pub/Report/2007/JC1399_ethical_considerations_en.pdf [Accessed July 2011].

UNAIDS 2010b. *2010: a Global view of HIV infection*. Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at: http://www.unaids.org/documents/20101123_2010_HIV_Prevalence_Map_em.pdf Accessed January 23, 2011.

UNAIDS 2010. *Global report: UNAIDS report on the global AIDS epidemic 2010.* Joint United Nations Programme on HIV/AIDS (UNAIDS) Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123_globalreport_en%5B1%5D.pdf Accessed Jan 23 2011.

UNAIDS. 2010a. *Good participatory practice guidelines for biomedical HIV prevention trials. Draft for public comment, Second edition,* Joint United Nations Programme on HIV/AIDS.

UNAIDS. 2010. Road-map agreed for confirmatory trials of promising microbicide. Geneva. Available at: http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2010/september/20100903prcaprisa [Accessed 5 March, 2013]

UNAIDS. 2011 (second edition). Good participatory practice: Guidelines for biomedical HIV prevention trials 2011.Available at:

http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf

UNAIDS/ World Health Organization (WHO). 2012 (English original 2007, additional guidance point added 2012).UNAIDS／07.28E／JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS／WHO Guidance Document. Geneva: UNAIDS and World Health Organization. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf [Accessed 18 Feb 2013].

UNAIDS. 2012. Global report: UNAIDS report on the global AIDS epidemic 2012. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf Accessed 30 January 2013

UNAIDS/AVAC. Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials, 2nd ed .Geneva, Switzerland: UNAIDS/AVAC. Available at: http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/manual/2010/Guidelines_Biomedical_HIV_Prevention_2010_en.pdf. [Accessed: 29th July 2012]

United Nations. 2008. The Millennium Development Goals Report. New York. Available at: http://www.un.org/millenniumgoals/pdf/The%20Millennium%20Development%20Goals%20Report%202008.pdf [Accessed July 30 2012.]

United Nations. International Covenant on Economic, Social and Cultural Rights, article 12. Entry into force 3 January 1976 .Note that the US has never ratified this as it appears to mandate universal access to healthcare. Available at: http://www2.ohchr.org/english/law/cescr.htm [Accessed 3 March 2010]

USAID. HIV/AIDS Health profile: Sub-Saharan Africa. http://transition.usaid.gov/our_work/global_health/aids/Countries/africa/hiv_summary_africa.pdf

US Military HIV Research program. RV152: A Follow-up Study for RV144. Available at: http://www.hivresearch.org/media/pnc/9/media.549.pdf [Accessed 6 March 2013].

Vallely, A, C Shagi, S Kasindi, N Desmond, S Lees, B Chiduo, RJ Hayes, C Allen, and D Ross. 2007. The benefits of participatory methodologies to develop effective community dialogue in the context of a microbicide trial feasibility study in Mwanza, Tanzania. *BMC Public Health* 7:133.

Van Damme, L., G. Ramjee, M. Alary et al. 2002. Effectiveness of COL-1492, nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 360: 971 - 977.

Van Damme, L., R. Govinden, F.M.Mirembe, et al. 2008. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *New England Journal of Medicine* 359: 463 - 472.

Van Damme, L., A. Corneli, K. Ahmed, et al. 2012. Preexposure Prophylaxis for HIV Infection among African Women. *New England Journal of Medicine* 367 (5):411-422.

van den Berg, C., K. Lindenburg, R. Coutinho. 2010. In *Modern infectious diseases epidemiology: concepts, methods, mathematical models and public health*, edited by M. K. Alexander Krämer, Klaus Krickeberg. New York, Dordrecht, Heidelberg, London: Springer.

van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS. 2012 26(7):F13-9.

van Griensven, F., J. W. de Lind van Wijngaarden, S. Baral, and A. Grulich. 2009. The global epidemic of HIV infection among men who have sex with men. *Current Opinion in HIV and AIDS* 4 (4):300-307.

van der Graaf, R., and J. J. M. van Delden. 2009. What is the Best Standard for the Standard of Care in Clinical Research? *The American Journal of Bioethics* 9 (3):35-43.

Vanichseni, S., J.W. Tappero, P. Pitisuttithum, et al. 2004. Recruitment, screening and characteristics of injection drug users participating in the AIDSVAX(R)B/E HIV vaccine trial, Bangkok, Thailand. *AIDS* 18 (2):311-316.

Varmus, H., and D. Satcher. 1997. Ethical Complexities of Conducting Research in Developing Countries. *New England Journal of Medicine* 337 (14):1003-1005.

Vermund, S. H. 1998. Rationale for the testing and use of a partially effective HIV vaccine. *AIDS research and human retroviruses* Suppl 3:S321-3.

Wade NA, Birkhead GS, Warren BL, et al. . 1998. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *New England Journal of Medicine* 339:1409--14. .

Weijer, Charles, and Guy J. LeBlanc. 2006. The balm of Gilead: is the provision of treatment to those who seroconvert in HIV prevention trials a matter of moral

obligation or moral negotiation? *Journal of Law, Medicine & Ethics* 34 (4):793(16).

Weijer, Charles, and Paul B. Miller. 2003. Another Voice: Therapeutic Obligation in Clinical Research. *The Hastings Center Report* 33 (3):3.

Whyte, B. Bulletin of the World Health Organization Nelson Mandela Calls for Unity at the XIIIth International AIDS Conference in Durban, South Africa., 2000,78 (9)p 1169. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2560854/pdf/0042-9686_78_9_1169a.pdf

Wheelock, A., A. B. Eisingerich, J.Ananworanich, et al. 2013. Are Thai MSM Willing to Take PrEP for HIV Prevention? An Analysis of Attitudes, Preferences and Acceptance. *PLoS ONE* 8 (1):e54288.

Women's Network for Unity. The tenofovir trial in Cambodia. 2008 [Short film on the internet]. Available at: http://www.drpetra.co.uk/blog/womens-network-for-unitys-account-of-the-tenofovir-trial then go to: http://blip.tv.file/1418090 [Accesse3 March 2010];

Wolinsky, H. The Battle of Helsinki.2006. *EMBO Reports* 7: 670-672

World Health Organization/UNAIDS. 2007. New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications. Montreux, Switzerland. Available at: http://libdoc.who.int/publications/2007/9789241595988_eng.pdf [Accessed 29 September 2012]

World Health Organisation. (WHO) 2010. New guidance on prevention of mother-to-child transmission of HIV and infant feeding in the context of HIV. Available at: http://www.who.int/hiv/pub/mtct/PMTCTfactsheet/en/index.html

World Health Organization. (WHO). 2012. Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Available at: http://www.who.int/hiv/PMTCT_update.pdf [Accessed 6 March 2013]

World Health Organisation. (WHO) 2012. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: Recommendations for use in the context of demonstration projects. July, 2012.Geneva, Switzerland: WHO. Available at: http://www.who.int/hiv/pub/guidance_prep/en/index.html [Accessed July 29th 2012].

World Health Organisation. April 2012. Programmatic Update: Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Executive summary. Available at: http://www.who.int/hiv/PMTCT_update.pdf [Accessed 20 November 2012]

World Health Organization/Joint United Nations Programme on HIV/AIDS (WHO/UNAIDS). The 3 by 5 initiative: Treat three million people with HIV/AIDS by 2005.[Report on the Internet] Available at: http://www.who.int/3by5/en/ [Accessed 21 February 2010]

World Health Organization. (WHO). 2012. Antiretroviral treatment access for the prevention of HIV and TB: 2012 Update. Available at: http://whqlibdoc.who.int/hq/2012/WHO_HIV_2012.12_eng.pdf Accessed 13 March 2013.

World Medical Association (WMA). 1948. *Declaration of Geneva*. Available at:

http://en.wikipedia.org/wiki/Declaration_of_Geneva (accessed February 6, 2013).

World Medical Association (WMA). Declaration of Helsinki. 1964; as amended in 2008. Available at: http://www.wma.net/en/30publications/10policies/10about/index.html Accessed 30 January 2013.

Zion, D. 2004. HIV/AIDS Clinical Research, and the Claims of Beneficence, Justice and Integrity. *Cambridge Quarterly of Healthcare Ethics*13:404-413

Complete reference list

References

Abdool Karim, Q., S. S. Abdool Karim, J. A. Frohlich, et al. 2010. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 329 (5996):1168-1174.

Abdool Karim S.S. and Q. Abdool Karim. 2011. Antiretroviral prophylaxis: A defining moment in HIV control. *Lancet* 378: e23-e25

ACT-UP New York. 2000. *Reports on the Durban International AIDS Conference.* Available at: http://www.actupny.org/reports/durban-who.html [Accessed 3 March 2010]

ACT-UP Paris, 2008. 'ACT-UP-Paris and treatment activism', http://www.actupparis.org/article3482.html [Accessed 12 September 2009].

AIDS 2010. 2010. Webcast: Safety and effectiveness of 1% Tenofovir Vaginal Microbicide Gel in South African Women: Results of of the CAPRISA 004 Trial. XVIII International AIDS Conference Vienna, ed. Available at: http://pag.aids2010.org/session.aspx?s=13#6 [Accessed 1 September 2013].

AIDS Vaccine Advocacy Coalition (AVAC). 2005. Will a pill a day prevent HIV? [Report on the internet], Available at: http://www.avac.org/ht/a/GetDocumentAction/i/3116 [Accessed 13 January 2010]

AIDS Vaccine Advocacy Coalition (AVAC). 2010. Frequently Asked Questions about PrEP and the iPrEx Trial.

AIDS Vaccine Advocacy Coalition (AVAC) 2010. November 23, 2010: p 6-7. Accessed 28 January 2011. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/31348

AIDS Vaccine Advocacy Coalition (AVAC). 2011. Frequently asked questions about FEM-PrEP. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/33632 Accessed 11 May 2011.

AIDS Vaccine Advocacy Coalition (AVAC). 2012. ARV-Based Prevention Options Timeline Available at: http://www.avac.org/ht/a/GetDocumentAction/i/46212 Accessed 5 March 2013.

AIDS Vaccine Advocacy Coalition (AVAC) Report. 2012. Achieving the end: One year and counting. Available at: http://www.avac.org/ht/d/sp/i/47457/pid/47457 [Accessed2 September 2013]

AIDS Vaccine Advocacy Coalition. (AVAC). 2012. AVAC Urges FDA Approval of PrEP Following Positive Advisory Committee Recommendation; Lays out Priorities to Ensure Access. Thursday, May 10, 2012. Available at: http://www.avac.org/ht/display/ReleaseDetails/i/43963/pid/212c [Accessed 14 May 2012]

AIDS Vaccine Advocacy Coalition (AVAC) N.D. PrEP Research to rollout: A schematic road map. Available at: http://www.avac.org/ht/a/GetDocumentAction/i/49134

Alcorn, K. 2005. Thai tenofovir trial runs into trouble after ethics protests from drug users. *Aidsmap* 2005.Available at:

http://www.aidsmap.com/en/news/AF0B8B91-A54B-4632-9736-03F66FE37CF5.asp

Accessed 14 January 2010.

Anderson, P.L., D. V. Glidden, A. Liu, et al. 2012. Emtricitabine-Tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Science Translational Medicine* 4 (151):151ra125

Anderson P., A. Liu, S. Buchbinder, et al; the iPrEx Study Team. 2012. Intracellular tenofovir-DP concentrations associated with PrEP efficacy in MSM from iPrEx.

Presented at: 19th Conference on Retroviruses and Opportunistic Infections; March 2012; Seattle, Washington

Anderson, R. M. and G. P. Garnett. 1996. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *Lancet* **348** (9033): 1010-1013.

Angell, M. 1997. The ethics of clinical research in the third world. *New England Journal of Medicine* 337 (12): 847-849.

Antiretroviral Therapy Cohort Collaboration. 2008. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: A collaborative analysis of 14 cohort studies. *Lancet* 372: 93-299

Ashcroft, R. 1999. Equipoise, knowledge and ethics in clinical research and practice. *Bioethics* 13(3-4): 314-326.

Ashcroft, R. E. 2004. Current epistemological problems in evidence based medicine. *Journal of Medical Ethics* 30 (2):131-135.

Auvert, B., D. Taljaard, E. Lagarde, J. Sobngwi-Tambekou, R. Sitta, and A. Puren. 2005. Randomized, controlled intervention trial of male circumcision for

reduction of HIV infection risk: The ANRS 1265 Trial. *PLoS Med* 2 (11):e298.

Baeten, J. M., D. Donnell, P. Ndase, et al. 2012. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *New England Journal of Medicine* 367 (5):399-410.

Bailey, R.C., S. Moses, C.B. Parker, et al. 2007. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 369:643 - 656.

Barr, D., J. J. Amon, M. Clayton. 2011. Articulating a rights-based approach to HIV treatment and prevention interventions. *Current HIV Research* 9 (6):396-404.

Bass, E. 2004. IIb or nor IIb: AIDS vaccine trial sponsors weigh the merits of intermediate-size efficacy trials. *IAVI Report* 8(1) Available at: http://www.iavireport.org/Back-Issues/Pages/IAVI-Report-08(1)-IIbornotIIb.aspx

Baume P. A question of balance: report on the future of drug evaluation in Australia. Canberra: Australian Government Publishing Service, 1991.

Bayer, R. 1989. Isolating the infected: the politics of control . *Private Acts, Social Consequences.* New York: The Free Press**:** 169-206.

Beauchamp, T., and J. Childress. 1994. *Principles of biomedical ethics*. 4th ed. New York, Oxford: Oxford University Press. Original edition, 1979.

Beecher, H. K. 1966. Ethics and Clinical Research. *New England Journal of Medicine* 274 (24):1354-1360.

Beloqui, J. 2008. International Rectal Microbicides Advocates: listserv communication. Available at: http://critpath.org/pipermail/rectalmicro_critpath.org/2008-November/000564.html [Accessed 13 January 2010]

Belsky, L., and H. S. Richardson. 2004. Medical researchers' ancillary clinical care responsibilities. *British Medical Journal* 328 (7454):1494-1496.

Benatar, S. R. 2001. Justice and medical research: A global perspective. *Bioethics* 15 (4):333-340.

Benatar, S.R., and P.A. Singer. 2000. A new look at international research ethics. *British Medical Journal* 321:824 - 826.

Bhaskaran, K. 2008. Changes in the Risk of death after HIV seroconversion compared with mortality in the general population. *Journal of the American Medical Association*, 300: 51-59

Bloom B. R. 1998. The highest attainable standard: Ethical issues in AIDS vaccines. *Science* 279: 186-188.

Boily,M.C. R. F. Baggaley, L.Wang, et al. 2009. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infectious Diseases* 9:118-29

Bright P.L. and R.M. Nelson. 2012. A capacity-based approach for addressing ancillary care needs: implications for research in resource limited settings. *Journal of Medical Ethics* 38(11):672-6.

Buchbinder, S. P., D.V. Mehrotra, A. Duerr, et al. 2008. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet* 372 (9653):1881-1893.

Cardo, D. M., D. H. Culver, C. A. Ciesielski, et al. 1997. A case–control study of HIV seroconversion in health care workers after percutaneous exposure. *New England Journal of Medicine* 337 (21):1485-1490.

Carrese, J.A., J. Sugarman. 2006. The inescapable relevance of bioethics for the

practicing clinician. *Chest*130(6):1864-72.

Celum, C., and J. Baeten. 2012. Tenofovir-based pre-exposure prophylaxis for HIV prevention: evolving evidence. *Current Opinion in Infectious Diseases:* 25 (1):51–57 doi: 10.1097/QCO.0b013e32834ef5ef

Centers for Disease Control. 1999. Case-Control Study of HIV seroconversion in health-care workers after percutaneous exposure to HIV infected blood- France, United Kingdom, and United States, January 1988-August 1994, *Morbidity and Mortality Weekly Report* 44:929-33

Centers for Disease Control. 2010. Pre-Exposure Prophylaxis (PrEP) for HIV Prevention: Promoting Safe and Effective Use in the United States. Press statement. November 23, 2010.

Available at:

http://www.cdc.gov/nchhstp/newsroom/PrEPforHIVFactSheet.html

Accessed January 23, 2010.

Centers for Disease Control. 2011. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. *Morbidity and Mortality Weekly Report* 60(03): 65-68.

Centers for Disease Control. (CDC). 2012. CDC Issues Interim Guidance on Use of Medication to Prevent HIV Infection among Heterosexually Active Adults. (News release)August 9 2012. Atlanta, GA: CDC. [Accessed October 14 2012]

Available at: http://www.cdc.gov/nchhstp/newsroom/2012/PrEP-HeterosexualGuidance-PressRelease.html

Centre for the AIDS Programme of Research in South Africa (CAPRISA). CAPRISA 008 MCC Correspondence: Sequence of Events; Q. Abdool Karim, S.S

Abdool Karim & L. Mansoor. Letter to Dr Portia Nkambule, Medicines Control Council. 22 March 2012.

Chua, A. N. Ford & D. Wilson, et al. 2005. The Tenofovir Pre-Exposure Prophylaxis Trial in Thailand: Researchers Should Show More Openness in Their Engagement with the Community, *PLoS Med* 2: 1044-1045

Cohen, M. S., Y. Q. Chen, M. McCauley, et al. 2011. Prevention of HIV-1 infection with early antiretroviral therapy. *New England Journal of Medicine* 365 (6):493-505.

Cohen, M. S., M. McCauley, and J. Sugarman. 2012. Establishing HIV treatment as prevention in the HIV Prevention Trials Network 052 randomized trial: an ethical odyssey. *Clinical Trials* 9(3):340-34

Compher, C. 2010. Efficacy vs effectiveness. *Journal of Parenteral and Enteral Nutrition*. 34(6): 598-599.

Connor, E. M., R. S. Sperling, R. Gelber, et al. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine* 331 (18):1173-1180.

CONRAD. 2010. FDA and CONRAD Chart U.S. Regulatory Path for 1% Tenofovir Gel for HIV Prevention: FDA has granted Fast Track approval designation for 1% tenofovir gel. Press statement. 25 October, 2010. Available at: http://www.natap.org/2010/newsUpdates/110110_01.htm Accessed January 23, 2010.

CONRAD. FDA and CONRAD Chart U.S. Regulatory Path for 1% Tenofovir Gel for HIV Prevention: Collaborative meeting held with key stakeholders. 2010. Available at:

http://www.conrad.org/media/news/88_CONRAD%20FDA%20Meeting%20Release%2020%20Final.doc. [Accessed 6 March 2013].

Cooper, E.R. M. Charurat, L. Mofenson, et al. 2002. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *Journal of Acquired Immune Deficiency Syndromes* 2002; 29: 484-494

Council for International Organizations of Medical Sciences (CIOMS). 2002. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available at: http://www.cioms.ch/publications/layout_guide2002.pdf Accessed 23 March 2013.

Council of Europe's Steering Committee on Bioethics (CDBI). Available at: http://www.coe.int/t/dg3/healthbioethic/cdbi/default_en.asp Accessed 23 March 2013.

Davis, M. 2008. The 'loss of community' and other problems for sexual citizenship in recent HIV prevention. *Sociology of Health & Illness* 30 (2):182-196.

De Zulueta, P. 2001. Randomised placebo-controlled trials and HIV-infected pregnant women in developing countries: Ethical imperialism or unethical exploitation? *Bioethics* 15 (4):289-311.

de Zoysa, I., C.J. Elias, & M.E. Bentley. 1998. Ethical challenges in efficacy trials of vaginal microbicides for HIV prevention. *American Journal of Public Health* 88(4): 571-5

Diarra, A. 2001. Making a public-private partnership work - an insider's view. Bulletin of the World Health Organization 79: 795-796

Donnell, D. 2012. Changes in detectable plasma levels over time in a pre-exposure prophylaxis clinical trial: the Partners PrEP study. (Conference paper) Microbicides 2012, April 20 2012.

Edgar, H. and D. Rothman, D. 1990. New rules for new drugs: The challenge of AIDS to the regulatory process. *Milbank Quarterly* 68, Suppl 1: 111-142.

Essack, Z., C. Slack, J. Koen, and G. Gray. 2010. HIV prevention responsibilities in HIV vaccine trials: Complexities facing South African researchers. *South African Medical Journal* 100 (1):45-48.

European Group on Ethics in Science and New Technologies (EGE). Available at: European Group on Ethics in Science and New Technologies. Accessed 23 March 2013.

Fawkes, J. The Cambodian PrEP trial: The sex workers' perspective. [Powerpoint presentation]. *The 2nd symposium on microbicides and HIV biomedical prevention*, Sydney, July 14, 2008.

Feldblum, P.J., A. Adeiga, R. Bakare, et al. 2008. SAVVY vaginal Ggel (C31G) for prevention of HIV infection: A randomized controlled trial in Nigeria. *PLoS ONE* 3: e1474

Fitzgerald, D.W., J.W. Pape, J.N. Wasserheit, G.W. Counts, and L. Corey. 2003. Provision of treatment in HIV-1 vaccine trials in developing countries. *Lancet* 362: 993–994.

Fleming, T. 2013. Non-inferiority clinical trials. Some key consideration in PrEP and microbicide studies. Presentation at the meeting on the Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues, Washington, January 7, 2013

http://www.hivforum.org/storage/hivforum/documents/FutureofPrEP/session_2_fleming.pdf [Accessed February 1, 2013]

Flynn, N. M., D. N. Forthal, C. D. Harro, et al. 2005. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *The Journal of infectious diseases* 191 (5):654-65.

Food and Drug Administration. (FDA). 2012. FDA Approves First Drug for Reducing the Risk of Sexually Acquired HIV Infection. (News release) July 16 2012. Silver Spring, MD: FDA. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm [Accessed September 10, 2012]

Food and Drug Administration. (FDA). 2012 Meeting Materials Antiviral Advisory Committee. May 11 2012 meeting of the Antiviral Drug Advisory Committee Questions to the committee available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM305774.pdf [Accessed 6 Oct 2012]

Transcript of meeting available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM311519.pdf [Accessed 6 Oct 2012]

All meeting materials available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm295937.htm [Accessed 6 Oct 2012]

Forbes, A. and S. Mudaliar. 2009. Preventing prevention trial failures: A case study and lessons learned for future trials from the 2004 tenofovir trial in Cambodia. Washington: Global Campaign for Microbicides.

Forbes A., Moving towards assured access to treatment in microbicide trials. 2006. *PLoS Medicine* 3 (7), e153: 980-983

Freedman, B. 1987. Equipoise and the ethics of clinical research. *New England Journal of Medicine* 317(3): 141-145.

Fried C. 1974. *Medical experimentation: personal integrity and social policy*. Amsterdam: North-Holland Publishing.

Geffen, N. What Happened in Durban? A South African Perspective. Gay Men's Health Crisis. September/October 2000.[Report on the Internet] Available at The Body http://www.thebody.com/content/art13213.html [Accessed 21 February 2010].

Gibbs J. Verdict on a virus. IRMA Rectal Microbicides Advocacy blog. http://irma-rectalmicrobicides.blogspot.com.au/2011/11/pros-and-cons-of-treatment-as.html [Accessed July 31 2012].

Gilbert, P.B. J.O. Berger, D. Stablein, et al. 2011. Statistical interpretation of the RV144 HIV vaccine efficacy trial in Thailand: A case study for statistical issues in efficacy trials. *Journal of Infectious Diseases* 203: 969-975

Global Campaign for Microbicides. Statement on FDA Regulatory Pathway for 1% Tenofovir Available at: http://www.globalcampaign.org/clientfiles/CONRAD%20FDA%20TFV%20GCM%20Statement.doc. Accessed 1 December 2010.

Global Network of People Living with HIV. About the global criminalisation scan. Available at: http://www.gnpplus.net/criminalisation. Accessed July 31, 2012.

Grant, R. M. 2010. Antiretroviral agents used by HIV-uninfected persons for prevention: Pre- and postexposure prophylaxis. *Clinical Infectious Diseases* 50(Supplement 3): S96-S101.

Grant, R. M., J. R. Lama, P. L. Anderson, et al. 2010. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine* 363 (27):2587-2599.

Gray, G., S. Buchbinder and A. Duerr. 2010. Overview of STEP and Phambili trial results: two phase IIb test-of-concept studies investigating the efficacy of MRK adenovirus type 5 gag/pol/nef subtype B HIV vaccine. Current Opinion in HIV AIDS. 5(5):357-61.

Gray, R.H., G. Kigozi, D. Serwadda, et al. 2007. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 369:657 - 666.

Haire B.G. Because we can: Clashes of perspective over obligation in the failed PrEP trials. *Developing World Bioethics* 2011;11: 63-74

Haire, B. 2011. Treatment-as-prevention needs to be considered in the just allocation of HIV drugs. *American Journal of Bioethics* 11 (12):48-50.

Haire, B., J. Kaldor, and C. F. C. Jordens. 2012. How good is “good enough”? The case for varying standards of evidence according to need for new interventions in HIV prevention. *American Journal of Bioethics* 12 (6):21-30.

Hankins, C.A., M.R. Dybul. 2013.The promise of pre-exposure prophylaxis with antiretroviral drugs to prevent HIV transmission: a review. *Current Opinion in HIV/AIDS* 8(1):50-8.

Hankins, C., R. Macklin, N. Michael, D. Stablein and participants. Meeting Report. Recommendations for the Future Utility of the RV144 Vaccines to the Thai Ministry of Health. March 16-18, 2010.

Heise, L.L., C.Watts, A. Foss, et al. 2011. Apples and oranges? Interpreting success in HIV prevention trials. *Contraception* 83 (1):10-15..

Heise,L., K. Shapiro and K. West Slevin. 2008. Mapping the Standards of Care at Microbicide Clinical Trial Sites. Washington DC: Global Campaign for Microbicides.

Heywood, Mark. 2009. South Africa's Treatment Action Campaign: Combining Law and Social Mobilization to Realize the Right to Health. *Journal of Human Rights Practice* 1 (1):14-36.

Holt, M., D.A. Murphy, D. Callander et al. Willingness to use HIV pre-exposure prophylaxis and the likelihood of decreased condom use are both associated with unprotected anal intercourse and the perceived likelihood of becoming HIV-positive among Australian gay and bisexual men. *Sexually Transmitted Infections*, 2012; 88, 258-263

Hirnschall, G., and B. Schwartländer. 2011. Treatment 2.0: catalysing the next phase of scale-up. *Lancet* 378 (9787):209-211.

HIV Vaccine Trials Network (HVTN) 505 Study. *HVTN 505: Expansion in Response to an Evolving Field.* Seattle, WA: HVTN Available at: http://hvtnews.wordpress.com/2011/09/13/hvtn-505-expansion-in-response-to-an-evolving-field/ [Accessed October 31 2012]

IAVI. Understanding Vaccine Licensure: What factors do regulatory bodies consider before licensing a vaccine for public use? Vax 2009; 7 (12).

Available at: http://www.vaxreport.org/Back-Issues/Pages/UnderstandingVaccineLicensure.aspx

[Accessed 7 March 2013].

Ipergay Study. http://www.ipergay.fr

International Conference on Harmonization Good Clinical practice (ICH-GCP). 1996. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf Accessed 23 March 2013.

International Planned Parenthood Federation, Global Network of People Living with HIV/AIDS, International Community of Women Living with HIV/AIDS. HIV - Verdict on a virus: Public health, human rights and criminal law. 2008. Available at: http://www.gnpplus.net/images/stories/2008_verdict_on_a_virus.pdf. Accessed July 31, 2012

International Rectal Microbicide Advocates. 2010. *From Promise to Product: Advancing Rectal Microbicide Research and Advocacy*. Pittsburgh, IRMA.

Jaffe, H. W. and T. Hope. 2010. Treating for the common good: A proposed ethical framework. *Public Health Ethics* 3(3): 193-198.

James, J.S. Access to treatment worldwide: From talk to action at Durban *Aids Treatment News* 2000. Issue #347, July 28. Available at: http://www.aegis.org/pubs/atn/2000/ATN34703.html Accessed 21 February 2010

Jansen, L. A. 2005. A closer look at the bad deal trial: Beyond clinical equipoise. *Hastings Center Report* **35**(5): 29-36. Accessed 2 February 2013

Jintarkanon, S., S. Nakapiew, and N. Tienudom, et al. 2005. Unethical clinical trials in Thailand: A Community Response (letter). *Lancet* 365: 1617-1618

Joffe, S., and F. G. Miller. 2012. Equipoise: asking the right questions for clinical trial design. *Nature Reviews Clinical Oncololgy* 9 (4):230-235.

Jonsen A.R. Bentham in a box: Technology and healthcare allocation. *L Med & Healthcare* 1986; **14**:172- 174

Kahn, J. O., J. N. Martin, M. E. Roland, J.D. Bamberger, M.Chesney, D. Chambers, K. Franses, T.J. Coates, and M.H. Katz. 2001. Feasibility of postexposure prophylaxis (PEP) against human immunodeficiency virus infection after sexual or injection drug use exposure: The San Francisco PEP Study. *Journal of Infectious Diseases* 183 (5):707-714.

Kaldor, J.M. and D.P. Wilson. 2010. How low can you go: the impact of a modestly effective HIV vaccine compared with male circumcision. *AIDS*; 24: 2573-2578 10.1097/QAD.0b013e32833ead96.

Kilmarx, P. H.,G. Ramjee, D. Kitayaporn, and P.Kunasol. 2001.Protection of human subjects' rights in HIV preventive clinical trials in Africa and Asia: Experiences and recommendations. *AIDS* 15(supplement 4): S1–S7

Kippax, S. N. Stephenson. 2012. Beyond the distinction between biomedical and social dimensions of HIV. *American Journal of Public Health* 102 (5):789-799.

Knox, R. and M. Doucleff. 2012. Clinton Reveals Blueprint For An 'AIDS-Free Generation'. *Shots: Health News*, http://www.npr.org/blogs/health/2012/11/29/166154269/clinton-reveals-blueprint-for-an-aids-free-generation.

Kopelman, L. 1986. Consent and randomised clinical trials: are there moral or design problems? *Journal of Medicine and Philosophy* 11: 317-345.

Kwidini, Tidi. 2012. Uganda's president dismisses circumcision, HIV research. *Zimeye*, 4 August 2012. Available at: http://www.zimeye.org/?p=58997 [Accessed 31 August 2013]

Lange, J.M. 2005. We must not let protestors derail trials of pre-exposure prophylaxis for HIV. *PLoS Medicine* 2: 833-834. Available at: http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.0020248

Le, T., E. J. Wright, D. M. Smith, et al. 2013. Enhanced CD4+ T-Cell recovery with earlier HIV-1 antiretroviral therapy. *New England Journal of Medicine* 368 (3):218-230.

Lemmens, T., and P. B. Miller. 2002. Avoiding a Jekyll-And-Hyde approach to the ethics of clinical research and practice. *American Journal of Bioethics* 2 (2):14-17.

Levine, R. J. 1999. The need to revise the Declaration of Helsinki. *New England Journal of Medicine* 341 (7):531-534.

Little M. "Better than numbers . . ." A gentle critique of evidence-based medicine. *Aust N Z J Surg* 2003; 73: 177-182.

Lissouba, P., D. Taljaard, D. Rech, et al. A model for the roll-out of comprehensive adult male circumcision services in African low-income settings of high HIV incidence: The ANRS 12126 Bophelo Pele Project. *PLoS Medicine* 2010; 7: e1000309.

Lo, B., N. Padian and M. Barnes. 2007. The obligation to provide antiretroviral treatment in HIV prevention trials. *AIDS* 21: 1229-1231.

Loff, B., J. Black. 2000. The Declaration of Helsinki and research in vulnerable populations. *Medical Journal of Australia* 172: 292-295

Loff, B. C. Jenkins & M. Ditmore et al. 2005. Letter to the editor (untitled), *Lancet* 365: 1618-1619

London, A. J. 2000. The ambiguity and the exigency: Clarifying 'standard of care' arguments in international research. *Journal of Medicine and Philosophy* 25 (4):379-397.

London, A., and K. Zollman. 2010. Research at the auction block: Problems for the fair benefits approach to international research. *Hastings Center Report*, 40(4): 34-45.

Lundgren, J. D., A. Babiker, W. El-Sadr, S. Emery, B. Grund, J. D. Neaton, J. Neuhaus, and A. N. Phillips. 2008. Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4+ Cell counts and HIV RNA levels during follow-up. *Journal of infectious diseases* 197 (8):1145-1155.

Lurie, P., and S. M. Wolfe. 1997. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine* 337 (12):853-856.

McCormack, S. Perspectives of a clinical researcher at the stage of grant writing. Standards of care in Future Microbicides Research Symposium. Presentation at the M2012 symposium. Microbicide 2012, Sydney, Australia. April 15th to 19th, 2012.

McGrory, E., A. Irvin, L. Heise. 2009.*Research Rashomon: Lessons from the Cameroon Pre Exposure Prophylaxis Trial Site. Washington, DC: Global Campaign for Microbicides at PATH; Available at: www.globalcampaign.org/clientfiles/Cameroon.pdf. Accessed: 8 January 2011.*

McGrory E, S. Philpot, C. Hankins, L. Paxton, L. Heise. 2010. *Standards of Prevention in HIV Prevention Trials: Consultation Report and Recommendations.* Washington DC, Global Campaign for Microbicides at PATH.

Macklin, R. 1999. *Against relativism : cultural diversity and the search for ethical universals in medicine*. New York: Oxford University Press.

Macklin, R. 2001. After Helsinki: Unresolved issues in international research. *Kennedy Institute of Ethics Journal* 11 (1):17-36.

Macklin, R. 2004. *Double standards in medical research in developing countries.* Cambridge; New York: Cambridge University Press.

Macklin, R. 2004. Striving for a single standard in *Double Standards in Medical Research in Developing Countries* Cambridge; New York Cambridge University Press, pp101-102.

Macklin, R. 2006. Changing the presumption: Providing ART to vaccine research participants. *American Journal of Bioethics* 6 (1):1 - 5.

Macklin, R. 2008. Standard of care: an evolution in ethical thinking. *Lancet* 372 (9635):284-285.

Macklin, R., 2011. Ethical challenges in HIV microbicide research: What protections do women need? *International Journal of Feminist Approaches to Bioethics* 2011; 4: 124-142, 128.

McNeill, D.G. 2000. Agencies urge use of affordable drug for HIV in Africa. *New York Times* (online.) 6 April. Available at http://www.nytimes.com/2000/04/06/world/agencies-urge-use-of-affordable-drug-for-hiv-in-africa.html?pagewanted=1 [Accessed 13 January 2010]

Mail & Guardian staff reporter. 2011. Trial of HIV-prevention gel enters final phase. *Mail & Guardian*, 14 June 2011. Available at: http://mg.co.za/article/2011-06-14-trial-of-hivprevention-gel-enters-final-leg [Accessed 2 September 2013]

Mann, J. M. 1997. Medicine and public health, ethics and human rights. *Hastings Center Report* 27 (3):6-13.

May M., M. Gompels and C. Sabin. 2012. *Life expectancy of HIV-1-positive individuals approaches normal, conditional on response to antiretroviral therapy: UK collaborative HIV cohort study*. Eleventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract O133, 2012.

Mayer, K. 2013. Future of PrEP and microbicide research: Setting the stage. Presentation at the meeting on the Future of PrEP and Microbicide Research: Trial Design and Regulatory Issues, Washington, January 7, 2013. Available at: http://www.hivforum.org/storage/hivforum/documents/FutureofPrEP/session_1_mayer.pdf [accessed February 2, 2013]

Marrazzo, J., G. Ramjee, G. Nair, et al. 2013.Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine or vaginal tenofovir gel in the VOICE study (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 26LB, 2013.

Medical Research Council (MRC). 2003. Policy on antiretroviral therapy (ART). Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002455 [Accessed 23 March 2013].

Medical Research Council (MRC). 2004. Research Involving Human Participants in Developing Societies. Available at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002461 [Accessed 23 March 2013].

Merkatz, R. & S. W. Junod. 1994. The historical background of changes in FDA policy on the study and evaluation of drugs in women. *Academic Medicine* 69(9): 703-7.

Merritt M. and C. Grady. 2006. Reciprocity and post-trial access for participants in antiretroviral therapy trials. *AIDS*; 20: 1791–1794

Microbicides Trial Network. Protocol. 2010 MTN-003 Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women (VOICE). Version 2. Available at: http://www.mtnstopshiv.org/sites/default/files/attachments/MTN003_FINAL_Version_2.0_31DEC200.pdf Accessed 5 March 2013

Microbicides Trials Network (MTN). 2011. Questions and Answers. Decision to Modify Voice: Outcome of November 17 Data and Safety Monitoring Board (DSMB) Review of Voice. November 17, 2011. Available at: http://www.mtnstopshiv.org/node/3908. Access 30 January 2013.

Microbicides Trial Network. 2011. MTN Statement on Decision to Discontinue Use of Oral Tenofovir Tablets in VOICE, a Major HIV Prevention Study in Women. September 28, 2011. Pittsburgh, PA: MTN. Available at: ***http://www.mtnstopshiv.org/node/3619*** [Accessed 24 September 2012]

Microbicides Trial Network. 2011.MTN Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women. Nov 25, 2011. Pittsburgh, PA: MTN Available at: http://www.mtnstopshiv.org/node/3909[Accessed 24 September 2012]

Microbicide Trials Network. (MTN). 2013. Understanding the results of VOICE. Available at: http://www.mtnstopshiv.org/news/studies/mtn003 Accessed 12 March 2013.

Miller, F. G. and H. Brody. 2003. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *The Hastings Center Report* 33(3): 19-28.

Miller, F.G. and H. Brody. 2003. The clinician-investigator: Unavoidable but manageable tension. *Kennedy Institute of Ethics Journal* 13 (4):329-346

Miller, F. G., and H. Brody. 2007. Clinical equipoise and the incoherence of research ethics. *Journal of Medicine and Philosophy* 32 (2):151-165.

Miller, F. G., and S. Joffe. 2011. Equipoise and the dilemma of randomized clinical trials. *New England Journal of Medicine* 364 (5):476-480.

Miller J. and B. Glasner. 2004. The "Inside" and the "Outside": Finding realities in interviews in D. Silverman (ed) *Qualitative Research: Theory, Method and Practice*. London: Sage, 2004: 125-129

Miller, P. B., and C. Weijer. 2006. Fiduciary obligation in clinical research. *The Journal of Law, Medicine & Ethics* 34 (2):424-440.

Miller, P. B., Weijer, C. 2007. Equipoise and the duty of care in clinical research: A philosophical response to our critics. *Journal of Medicine and Philosophy* 32(2): 117-133.

Mills, E., S. Singh, J. Singh et al. 2005. Designing research in vulnerable populations: Lessons from the HIV prevention trials that stopped early. *British Medical Journal*, 331: 1403-1406

Mills, E., B. Rachlis, P. Wu, et al. 2005.Media reporting of tenofovir trials in Cambodia and Cameroon. *BMC International Health and Human Rights* 5 (6).

Millum, J. 2011. Post-trial access to antiretrovirals: Who owes what to whom? *Bioethics* 25: 145154

Minister of Health and Others v Treatment Action Campaign and Others (No 1) (CCT9/02) [2002] ZACC 16; 2002 (5) SA 703; 2002 (10) BCLR 1075 (5 July 2002). http://www.saflii.org/za/cases/ZACC/2002/16.html

Moatti, J.P., I. N'Doye & S. M. Hammer et al. 2003. Antiretroviral treatment for HIV infection in developing countries: An attainable new paradigm. *Nature Medicine* 9: 1449-52.

Musacchio, N. S., M. Hartrich, and R. Garofalo. 2006. Erectile dysfunction and viagra Use: What's up with college-age males? *Journal of Adolescent Health* 39 (3):452-454.

National Bioethics Advisory Commission (NBAC). 2001. Ethical and policy issues in international research: Clinical trials in developing countries. Bethesda, Maryland. Available at: http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf Accessed 23 March 2012.

The National Committee to Review Current Procedures from Approval of New Drugs for Cancer and AIDS (Lasagna Commission) *Final Report* (August 15 1990).

Ndebele, P., D. Wassenaar, E. Munalula and F. Masiye. 2012. Improving understanding of clinical trial procedures among low literacy populations: an intervention within a microbicide trial in Malawi. *BMC Medical Ethics* 13: 29.

New HIV Vaccine and Microbicides Advocacy Society (NHVMAS). 2012. Research Community Request For Better Process Of Community Engagement, Informed Consent And Standard Of Care in HIV Research in Nigeria. Lagos, Nigeria:NHVMAS. Available at: http://nhvmas-ng.org/website/eventcontent.php?eventid=%20141 [Accessed 18 February 2013]

New York Department of Health. 1999.Confidence intervals: statistics teaching tools. Available at: http://www.health.state.ny.us/diseases/chronic/confint.htm Accessed 26 April 2011.

Nuffield Council on Bioethics. 2007. *Public health: ethical issues*. Chapter 2 (An Ethical Framework) Available at: http://www.nuffieldbioethics.org/sites/default/files/files/Public%20health%20Chapter%202%20-%20An%20ethical%20framework.pdf Accessed 23 March 2013.

Nuffield Council on Bioethics. 2005. The ethics of research related to healthcare in developing countries: a follow-up discussion paper. Out of print.

Nunn, A., S. McCormack, A. Crook, R. Pool, C. Rutterford and R. Hayes. 2009. Microbicides Development Programme: design of a phase III trial to measure the efficacy of the vaginal microbicide PRO 2000/5 for HIV prevention. *Trials* 10(1): 99

O'Connor, C. C., G. Berry, R. Rohrsheim, and B. Donovan. 1996. Sexual health and use of condoms among local and international sex workers in Sydney. *Genitourinary Medicine* 72 (1):47-51.

Padian, N.S., A. Buvé, J. Balkus, D., Serwadda, W. Cates Jr. 2008. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. *Lancet.* 372(9638):585-99.

Padian, N.S., A. Straten, G. Ramjee, et al. 2007. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomized controlled trial. *Lancet* 370:251 - 261.

Page-Shafer, K., V. Saphonn, L. P. Sun, et al. 2005. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. *Lancet* 366 (9495):1499-1503.

Panel on Antiretroviral Guidelines for Adults and Adolescents. 2013. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 11 March 2012.

Pantaleo, G., M. Esteban, B. Jacobs & J. Tartaglia. Poxvirus vector-based HIV vaccines. 2010.*Current Opinion in HIV and AIDS* 5: 391-396 10.1097/COH.0b013e32833d1e87.

Partners PrEP. Protocol Addendum #8, 28 July 2011. Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV -1 Acquisition within HIV-1 Discordant Couples. Version 3.0, 12 October 2007 p 2

Peterson, L., D. Taylor, R. Roddy, et al. 2007. Tenofovir disoproxil fumarate for prevention of HIV infection in women: A phase 2, double-blind, randomized, placebo-controlled trial. *PLOS Clinical Trials* 2 (5):e27.

Philpott, S., K. West Slevin, K. Shapiro, and L. Heise. 2010. Impact of donor-imposed requirements and restrictions on standards of prevention and access to care and treatment in HIV prevention trials. *Public Health Ethics* 3 (3):220-228.

Philpott, S., L. Heise, E. McGrory, et al. 2011. The challenge of defining standards of prevention in HIV prevention trials. *Journal of Medical Ethics* 37 (4):244-248.

Powers, M. 'Theories of justice in the context of research' in Jeffrey P Kahn, Anna Mastroianni, Jeremy Sugarman, ed. *Beyond Consent: Seeking Justice in Research*. 1998, Oxford University Press: Ox ford New York. 190.

Poynten, I.M., Jin, F., Mao, L.,et al. 2009. Nonoccupational postexposure prophylaxis, subsequent risk behaviour and HIV incidence in a cohort of Australian homosexual men *AIDS* 23 (9):1119-26.

Press release. Terms of deal to make gel affordable and accessible in Africa following regulatory approval. *Eureka Alert* 2010. Available at: http://www.hst.org.za/news/next-steps-tenofovir-gel-conrad-and-tia-sign-license-agreement [Accessed 5 March, 2013]

Protocol Addendum #8, 28 July 2011. Parallel Comparison of Tenofovir and Emtricitabine/tenofovir Pre-Exposure Prophylaxis to Prevent HIV -1 Acquisition within HIV-1 Discordant Couples. Version 3.0, 12 October 2007 p 2.

Ramjee G., A. Kamali, S. McCormack S. 2010. The last decade of microbicide clinical trials in Africa: from hypothesis to facts. *AIDS* Suppl 4:S40-9.

Rennie S., J. Sugarman and the HPTN Ethics Working Group. 2009. HIV Prevention Trials Network Ethics Guidance for Research, HIV Prevention Trials Network.

Rennie, S., and J. Sugarman. 2010. Developing ethics guidance for HIV prevention research: the HIV Prevention Trials Network approach. *Journal of Medical Ethics* 36 (12):810-815.

Rerks-Ngarm, S., P. Pitisuttithum, S.Nitayaphan, et al. 2009. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *New England Journal of Medicine* 361(23):2209-2220.

The Review Team for NDA 21-752/S-30. 2012. Memorandum TRUVADA (emtricitabine-tenofovir disoproxil fumarate). April 16, 2012. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM303213.pdf [Accessed 14 May 2012]

Richardson, H. S. 2007. Gradations of researchers' obligation to provide ancillary care for HIV/AIDS in developing countries. *American Journal of Public Health* 97(11):1956-1961

Roehr, B. Tenofovir works as pre-exposure prophylaxis against HIV, two studies confirm 2011. *British Medical Journal*. 343:d4540

Rosen, S., and M.P. Fox. 2011. Retention in HIV care between testing and treatment in sub-Saharan Africa: A systematic review. *PLoS Medicine* 8(7):e1001056.

rgp120 HIV Vaccine Study Group. 2005. *Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. rgp120 Vaccine Study Group.* J Infect Dis 191: 654-665.

RV144 Follow-up Study RV305 Begins in Thailand. November 4, 2012. Available at: http://www.hivresearch.org/news.php?NewsID=238 [Accessed 6 March 2013].

Schneider, H., D., Blaauw, L. Gilson, N. Chabikuli, and J. Goudge. 2006. Health systems and access to antiretroviral drugs for HIV in southern Africa: Service delivery and human resources challenges. *Reproductive Health Matters* 14 (27):12-23.

Schouten E.J., A. Jahn, D. Midiani, et al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. *Lancet* 2011; 378: 282–84

Schüklenk, U. 2010. Calling it a day on proceduralism in bioethics? *Bioethics* **24**(9): ii-ii.

Schroeder D. and E. Gefenas. 2011. Realising benefit sharing – The case of post-study obligations. *Bioethics* 26(6): 305-314.

Shapiro, K., and S.R. Benatar. 2005. HIV prevention research and global inequality: steps towards improved standards of care. *Journal of Medical Ethics* 31 (1):39 - 47.

Silverman J., M.R. Decker, N. Saggurti, D. Balaiah, and A. Raj. 2008. Intimate partner violence and HIV infection among married Indian women. *JAMA: Journal of the American Medical Association* 300 (6):703-710.

Singer, P. A., and S. R. Benatar. 2001. Beyond Helsinki: a vision for global health ethics. *British Medical Journal* 322 (7289):747-748.

Skoler-Karpoff, S., G. Ramjee, K. Ahmed, et al. 2008. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. *Lancet* 372:1977 - 1987.

Slack, C., M. Stobie, C. Milford, et al. 2005. Provision of HIV treatment in HIV preventive vaccine trials: a developing country perspective. *Social Science and Medicine* 60(6): 1197-1208.

South African Department of Health. Report on the 13th International AIDS Conference, Durban, 9 – 14 July 2000. Summary Report of Major Issues, Conclusions and Recommendations. [Report on the internet.] –section 7.3. Available at: http://www.doh.gov.za/aids/docs/13conf00.html

SPARTAC Trial Investigators. 2013. Short-Course antiretroviral therapy in primary HIV infection. *New England Journal of Medicine* 368 (3):207-217.

Stadler J., and E. Saethre. 2010. Blockage and flow: intimate experiences of condoms and microbicides in a South African clinical trial. *Culture, Health & Sexuality: An International Journal for Research, Intervention and Care* 13(1): 31-34.

START study. Available at: http://www.niaid.nih.gov/volunteer/hivandinfectious/hivstudies/Pages/STARTStudy.aspx. Accessed July 31 2012

Strategic Timing of Anti-Retroviral Treatment (START study) (2011) http://www.niaid.nih.gov/volunteer/hivandinfectious/hivstudies/Pages/STARTStudy.aspx.

Steinbrook R. 2006. Compensation for injured research subjects. *New England Journal of Medicine* 354: 1871-73

Strategies for Management of Antiretroviral Therapy Study Group.(SMART Study) (2008). Major clinical outcomes in antiretroviral therapy (ART)–naive participants and in those not receiving ART at baseline in the SMART Study. *Journal of Infectious Diseases* 2008 **197**(8): 1133-1144.

Stobie, M. and C. Slack. 2010. Treatment needs in HIV prevention trials: Using beneficence to clarify sponsor-investigator responsibilities. *Developing World Bioethics*. 10(3):150-7. doi: 10.1111/j.1471-8847.2009.00272.

Stone, A. 2009. *Regulatory Issues in Microbicide Development.* World Health Organisation.

Strubb, S. 2010. Medical ethics and the rights of people with HIV under assault. Poz Blogs, Poz. 2012.

Strubb, S. 2012. Public health or slippery slope? Poz Blogs, Poz. **2012**.

Thigpen, M. C., P. M. Kebaabetswe, L.A. Paxton, et al. 2012. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *New England Journal of Medicine* 367 (5):423-434.

Track C Session summary TUWS02. Implementing Pre-exposure Prophylaxis: Current Progress and Future Challenges. AIDS 2012. Available at: http://rapporteurs.aids2012.org/SummaryView.aspx?summary_id=187 Accessed 6 March 2013.

Treatment Action Campaign (TAC). TAC Briefing on Adult and Adolescent Voluntary Medical Male Circumcision (VMMC). Capetown, South Africa:TAC. Available at:

http://www.tac.org.za/community/node/3190 [Accessed 25 September 2012

Ukpong M.O. 2012 . Perspectives on Community Engagement in Standard of Prevention Package Negotiation for Clinical Trials. Presentation at the M2012 symposium. Microbicide 2012, Sydney, Australia, USA. April 15th to 19th, 2012.

Ukpong, M., and K. Peterson, eds. 2009. *Oral Tenofovir Controversy II: Voices from the Field*. Falomo, Nigeria: New HIV Vaccines and Microbicides Society (NHVMAS).

UNAIDS/WHO. 2007. Ethical considerations in biomedical HIV prevention trials [monograph on the Internet]. Joint United Nations Programme on HIV/AIDS (UNAIDS).

UNAIDS/World Health Organization (WHO). 2007.UNAIDS/07.28E/JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS/WHO Guidance Document. Geneva: UNAIDS and World Health Organization. Available at:http://data.unaids.org/pub/Report/2007/JC1399_ethical_considerations_en.pdf [Accessed July 2011].

UNAIDS 2010. *2010: a Global view of HIV infection*. Joint United Nations Programme on HIV/AIDS (UNAIDS). Available at: http://www.unaids.org/documents/20101123_2010_HIV_Prevalence_Map_em.pdf Accessed January 23, 2011.

UNAIDS. 2010. Road-map agreed for confirmatory trials of promising microbicide. Geneva. Available at: http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2010/september/20100903prcaprisa [Accessed 5 March, 2013]

UNAIDS. 2010a. *Good participatory practice guidelines for biomedical HIV prevention trials. Draft for public comment, Second edition*, Joint United Nations Programme on HIV/AIDS.

UNAIDS 2010b. *Global report: UNAIDS report on the global AIDS epidemic 2010.* Joint United Nations Programme on HIV/AIDS (UNAIDS)

Available at:

http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123_globalreport_en%5B1%5D.pdf Accessed Jan 23 2011.

UNAIDS. 2011 (second edition). Good participatory practice: Guidelines for biomedical HIV prevention trials 2011.Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf

UNAIDS/ World Health Organization (WHO). 2012 (English original 2007, additional guidance point added 2012).UNAIDS／07.28E／JC1349E Ethical Considerations in Biomedical HIV Prevention Trials. UNAIDS／WHO Guidance Document. Geneva: UNAIDS and World Health Organization. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf [Accessed 18 Feb 2013].

UNAIDS. 2012. Global report: UNAIDS report on the global AIDS epidemic 2012. Available at:

http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf

Accessed 30 January 2013

UNAIDS/AVAC. Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials, 2nd ed. Geneva, Switzerland: UNAIDS/AVAC. Available at:

http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/manual/2010/Guidelines_Biomedical_HIV_Prevention_2010_en.pdf. [Accessed: 29th July 2012]

United Nations. 2008. The Millennium Development Goals Report. New York. Available at: http://www.un.org/millenniumgoals/pdf/The%20Millennium%20Development%20Goals%20Report%202008.pdf [Accessed July 30 2012.]

United Nations. International Covenant on Economic, Social and Cultural Rights, article 12. Entry into force 3 January 1976 .Note that the US has never ratified this as it appears to mandate universal access to healthcare. Available at: http://www2.ohchr.org/english/law/cescr.htm [Accessed 3 March 2010]

USAID. HIV/AIDS Health profile: Sub-Saharan Africa. http://transition.usaid.gov/our_work/global_health/aids/Countries/africa/hiv_summary_africa.pdf

US Military HIV Research program. RV152: A Follow-up Study for RV144. Available at: http://www.hivresearch.org/media/pnc/9/media.549.pdf [Accessed 6 March 2013].

Vallely, A., C. Shagi, S. Kasindi, N. Desmond, S. Lees, B. Chiduo, R.J. Hayes, C. Allen, and D. Ross. 2007. The benefits of participatory methodologies to develop effective community dialogue in the context of a microbicide trial feasibility study in Mwanza, Tanzania. *BMC Public Health* 7:133.

Vallely, A., C. Shagi, S. Lees, et al. 2009. Microbicides Development Programme: Engaging the community in the standard of care debate in a vaginal microbicide trial in Mwanza, Tanzania. *BMC Medical Ethics* 10 (1):17.

Van Damme, L., G. Ramjee, M. Alary et al. 2002. Effectiveness of COL-1492, nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 360: 971 - 977.

Van Damme, L., R. Govinden, F.M. Mirembe, et al. 2008. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *New England Journal of Medicine* 359: 463 - 472.

Van Damme, L., A. Corneli, K. Ahmed, et al. 2012. Preexposure Prophylaxis for HIV infection among African women. *New England Journal of Medicine* 367 (5):411-422.

van den Berg, C., K. Lindenburg, R. Coutinho. 2010. In *Modern infectious diseases epidemiology: concepts, methods, mathematical models and public health*, edited by M. K. Alexander Krämer, Klaus Krickeberg. New York, Dordrecht, Heidelberg, London: Springer.

van der Graaf, R., and J. J. M. van Delden. 2009. What is the best standard for the standard of care in clinical research? *American Journal of Bioethics* 9 (3):35-43.

van der Straten, A., L. Van Damme, J.E. Haberer, D.R. Bangsberg. 2012. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS. 2012 26(7):F13-9.

van Griensven, F., J. W. de Lind van Wijngaarden, S. Baral, and A. Grulich. 2009. The global epidemic of HIV infection among men who have sex with men. *Current Opinion in HIV and AIDS* 4 (4):300-307.

Vanichseni, S., J.W. Tappero, P. Pitisuttithum, et al. 2004. Recruitment, screening and characteristics of injection drug users participating in the AIDSVAX(R)B/E HIV vaccine trial, Bangkok, Thailand. *AIDS* 18 (2):311-316.

Varmus, H., and D. Satcher. 1997. Ethical complexities of conducting research in developing countries. *New England Journal of Medicine* 337 (14):1003-1005.

Vermund, S. H. 1998. Rationale for the testing and use of a partially effective HIV vaccine. *AIDS research and human retroviruses* Suppl 3:S321-3.

Wade N.A., G.S. Birkhead, B.L. Warren, et al. 1998. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *New England Journal of Medicine* 339:1409--14. .

Weijer, C., and G. J. LeBlanc. 2006. The balm of Gilead: is the provision of treatment to those who seroconvert in HIV prevention trials a matter of moral obligation or moral negotiation? *Journal of Law, Medicine & Ethics* 34 (4):793(16).

Weijer, C., and P. B. Miller. 2003. Another voice: Therapeutic obligation in clinical research. *Hastings Center Report* 33 (3):3.

Whyte, B. Bulletin of the World Health Organization. Nelson Mandela Calls for Unity at the XIIIth International AIDS Conference in Durban, South Africa. 2000,78 (9)p 1169. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2560854/pdf/0042-9686_78_9_1169a.pdf

Wheelock, A., A. B. Eisingerich, J.Ananworanich, et al. 2013. Are Thai MSM willing to take PrEP for HIV prevention? An analysis of attitudes, preferences and acceptance. *PLoS ONE* 8 (1):e54288.

Women's Network for Unity. The tenofovir trial in Cambodia. 2008 [Short film on the internet]. Available at: http://www.drpetra.co.uk/blog/womens-network-for-unitys-account-of-the-tenofovir-trial then go to: http://blip.tv.file/1418090 [Accesse3 March 2010];

Wolinsky, H. The Battle of Helsinki.2006. *EMBO Reports* 7: 670-672

World Health Organization/UNAIDS. 2007. New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications. Montreux, Switzerland. Available at: http://libdoc.who.int/publications/2007/9789241595988_eng.pdf [Accessed 29 September 2012]

World Health Organisation. (WHO) 2010. New guidance on prevention of mother-to-child transmission of HIV and infant feeding in the context of HIV. Available at: http://www.who.int/hiv/pub/mtct/PMTCTfactsheet/en/index.html

World Health Organization. (WHO). 2012. Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Available at: http://www.who.int/hiv/PMTCT_update.pdf [Accessed 6 March 2013]

World Health Organisation. (WHO) 2012. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: Recommendations for use in the context of demonstration projects. July, 2012.Geneva, Switzerland: WHO. Available at: http://www.who.int/hiv/pub/guidance_prep/en/index.html [Accessed July 29th 2012].

World Health Organisation. April 2012. Programmatic Update: Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Executive summary. Available at: http://www.who.int/hiv/PMTCT_update.pdf [Accessed 20 November 2012]

World Health Organization/Joint United Nations Programme on HIV/AIDS (WHO/UNAIDS). The 3 by 5 initiative: Treat three million people with HIV/AIDS by 2005.[Report on the Internet] Available at: http://www.who.int/3by5/en/ [Accessed 21 February 2010]

World Health Organization. (WHO). 2012. Antiretroviral treatment access for the prevention of HIV and TB: 2012 Update. Available at: http://whqlibdoc.who.int/hq/2012/WHO_HIV_2012.12_eng.pdf Accessed 13 March 2013.

World Medical Association (WMA). 1948. *Declaration of Geneva*. Available at: http://en.wikipedia.org/wiki/Declaration_of_Geneva (accessed February 6, 2013).

World Medical Association (WMA). Declaration of Helsinki. 1964; as amended in 2008. Available at: http://www.wma.net/en/30publications/10policies/10about/index.html Accessed 30 January 2013

Worrall, J. 2002. What evidence in evidence-based medicine? *Philosophy of Science* 69(S3): S316-S330.

Zaynab E., J. Koen, N. Barsdorf, et al. 2010. Stakeholder perspectives on ethical challenges in HIV vaccine trials in South Africa. *Developing World Bioethics* 10 (1):11-21

Zion, D. 2004. HIV/AIDS Clinical research, and the claims of beneficence, justice and integrity. *Cambridge Quarterly of Healthcare Ethics*13:404-413

Appendices

Appendix A – Ethics approval letter

Appendix B – Participants information and consent forms

Investigators (telephone interview)

Investigators (face-to-face)

Survey (investigators)

Survey (ethics committee members)

Interview consent form

Appendix C – Related publications not included in this thesis:

Haire, B. 2009. Back to basics on standard of care. *American Journal of Bioethics* 9(3): 48-69

Haire, B. 2011. Treatment-as-prevention needs to be considered in the just allocation of HIV drugs. *American Journal of Bioethics* 11(12): 48-50

McGregor, S., G. Tachedjian, B. G. Haire, and J. M. Kaldor. 2013. The seventh (and last?) International Microbicides Conference: From discovery to delivery. *Sexual Health* 10 (3):240-245.

Appendix D – Survey results summaries:

Initial investigator report

Final investigator report

Ethics committee member report

This proposed research program will examine the interface between ethical constructs at a personal and societal level and a range of issues related to infectious disease control. It will address three distinct, but related issues in sexual health: the ethics of mass drug administration, personal ethics and sexual health, and the ethics of sexual representation.

Aims

1. **Mass drug distribution:** This project will explore the acceptability and feasibility of population-based distribution of drugs for endemic curable sexually transmissible infections (STIs) and pre-exposure prophylaxis for HIV. It will address the timely question of whether mass drug administration – an intervention proposed in populations at high risk of STIs, HIV and parasitic disease acquisition – is an acceptable and appropriate mechanism for controlling endemic STIs and their consequences in selected populations.
2. **Personal ethics and understandings of sexual health:** This project will ask how people at high risk of STIs understand 'sexual health', how they formulate their personal sexual ethics, and how this influences their sexual attitudes and practice.
3. **Ethics of sexual representation:** This project will consider how participants perceive mass media representations of bodies and sexuality, including pornographic genres, to affect their sexual attitudes, practice, ethics and self-image.

Rationale: These questions are important for policy development, particularly as it relates to the design and development of targeted sexual health interventions. Findings will guide such t interventions, ensuring they are framed in ways that make sense to the people for whom they are designed, avoid reinforcing negative stereotypes.

Background

1. Mass drug administration for curable STIs.

Mass drug administration is defined as the provision of a pharmacological agent that is therapeutically active against a particular infection to all members of a population, regardless of the individual presence of infection, with the goal of reducing transmission and prevalence of infection in the population. The strategy has appeal when health authorities are faced with endemic infections that do not respond to other forms of prevention, and or conventional approaches to treatment that target those in whom infection has actually been diagnosed. They are also controversial because they are seen as taking away autonomy of both patient and clinician, and undermining the individual's role and responsibility in disease control. Whether or not this loss of autonomy is balanced by the health benefits of reducing STI rates, is ultimately not a call that can be made by policy makers from outside the affected communities – these communities need to debate the issues and contribute to making a decision based on their own value systems.

Internationally, mass drug administration is widely used for endemic parasitic diseases. In Australia its role has so far been limited to endemic trachoma in remote Aboriginal communities, but it has been variously proposed and investigated for sexually transmitted infections, scabies and other conditions. However, there has been little research on attitudes and perceptions related to mass drug administration, either in Australia or the Asia-Pacific region.

Prior research also shows that mass drug distribution can control endemic STIs (e.g. Bollen et al 2010, Wiet al 2006; Mayaud and Mabey 2004; Wawer 1999). Mass drug distribution for STIs is an 'elimination of choice' public health strategy that requires strong justification to balance the diminution of autonomy that such a strategy necessarily involves. Other values may be more important than autonomy in particular circumstance, however, such as the lack of stigma associated with a community-wide program rather than individualised diagnosis and treatment of a disease perceived to be stigmatised. A mass drug distribution strategy cannot succeed without community consent. Its feasibility depends on whether communities will use the intervention, and recent experience in HIV research shows

that communities may now take up pill-taking intervention when there is no evident disease (Marrazzo et al 2013; van Damme et al 2012).

2. Understandings of sexual health.

How people understand their responsibility to sexual partners and how they then enact these understandings is critical to the control of STIs and HIV. Between 1975 and 2002, eight different definition of 'sexual health' have been identified in the literature, with more recent ones adding concepts of mental health, responsibility and sexual rights (Edwards and Coleman 2004). Concepts of personal responsibility, shared responsibility and 'special' responsibility have been debated at length over the three decades of the HIV epidemic (e.g. Bayer 1996, Adam 2005) but changes in treatment efficacy and the relationship between treatment and prevention have changed the way that HIV is understood, which may impact on ethical deliberations.

3.Relationships between representations of sex and sexuality in relation to sexual health.

Representation of sexual practice is a vexed issue in health. Pornography has been linked with social harm in some studies (e.g. Perrin et al 2008), but exonerated from it in others (Luder et al 2011). Critiques of health promotion campaigns and advertising generally, however, show that non-sexually explicit material may also be objectifying, demeaning and shaming (Carter et al 2011), or, conversely, portray idealised and exoticised images that may be experienced as deeply disenfranchising (Borgerson, J. L. and Schroeder, J. E. 2005). Sexual representation has been implicated in public health interventions in Australia and the US, including banning of pornography under the Northern Territory Intervention and the LA county law banning the making of pornography in which condoms are not used by the actors (Grudzen and Kerndt 2007). Sexualised representation is frequently used in health promotion targeting gay men, including images taken directly from pornography (Batrouney, personal communication) which raises profound ethical questions about objectification in health promotion. Strong negative connotations have been alleged between explicit pornography and sexual abuse, and censorship of such material has formed a part of the controversial Northern Territory Intervention that commenced under the Howard Government (Human Rights Watch 2007). Whether or not this aspect of the intervention was justified is unknown, however, and in addition, there are other genres, such as romance fiction, music videos and mass media, for example, that could have negative impacts upon understandings of gender roles, identity and sexual practice (Borgerson, J. L. and Schroeder, J. E. 2005).

Proposed research program

I will initiate and undertake a collaborative research program using qualitative research methods to investigate:

1. The understanding and perception of mass drug administration strategies; and the barriers and incentives to the uptake of the mass drug administration strategies for different infections (STIs, HIV and parasitic diseases) and populations (gay men, women involved in sex work and communities in the Pacific region).
2. Understandings and perception of sexual health and sexual health ethics; and
3. Sexual representation and its perceived impacts upon self-image, personal ethics, sexuality and sexual practice.

Methods

Each element of the program will involve interviews and focus groups with members of communities at high risk of STIs, HIV or parasitic disease acquisition, predominantly gay men and communities in the Pacific region including female sex workers. The mass drug distribution component will also involve interviews and focus groups with policy makers, clinicians and representatives of affected communities.

The sexual health and personal ethics component will use the eight different definitions of 'sexual health' identified by Edwards and Coleman (2004) to prompt discussion of key concepts including sexual rights, agency and responsibility.

The sexual representation component will recruit participants from communities who read gay and lesbian print media, and participants will be asked to view and respond to a range of images, including health promotion campaigns that use imagery sourced from pornography, and mainstream advertising for vodka and hosiery that includes sado-masochistic imagery and sexual violence. Analytic categories and concepts defined by Carter et al (2011), and Borgerson and Schroeder (2005) will also be used in the analysis of the ethics of sexual representation.

Reference groups consisting of members of the communities to be included in the research will be formed to guide the research, and this will occur in a timely fashion so that the reference groups can have real and meaningful input into the design of the research tools, in particular the semi-structured interview protocol. Involving the relevant communities in discussion about the proposed program and taking heed of their responses is a respectful and appropriate way of addressing ethical issues in sexual health.

Data will be coded using NVivo9 software and analysed using an inductive grounded theory approach. Descriptive data will be analysed using three different ethical constructs: the Nuffield public health stewardship approach (Nuffield Council of Bioethics 2007), principle-ism (Beauchamp and Childress 1994) and Martha Nussbaum's capabilities approach (2000). Each of these three ethical frameworks seeks to balance communitarian and individual benefits.

Significance

1. This mass drug distribution component of this proposal will answer a question of public health significance that is in some respects confounded by its ethical sensitivity. The ethical issues around pre-exposure prophylaxis (PrEP) for HIV and population-based presumptive treatment are quite distinct. With regard to PrEP, the issue is whether provision of this form of HIV prevention to individuals at particularly high risk of HIV acquisition could result in community harm through the undermining of safe sex cultures and a growing dependency upon a prevention strategy of lower biological efficacy than condom-based prevention. The issue with population-based STI treatment is that it undermines individual agency and subjects some individuals to an unnecessary pharmacological intervention, with its attendant risks, for the presumed benefit of others. While there is evidence that PrEP is biologically effective (Grant et al 2010, Anderson et al 2012, Baeten et al 2012), it has also failed in some trial settings due to poor compliance (van Damme 2012, Marrazzo 2013). This raises an additional ethical issue of appropriate health resource allocation.
2. Enquiry into the meaning of sexual health and sexual health ethics is necessary if we are to understand the complexity of human sexual behaviour. This study explores ethical frameworks perceived and described by participants –their own, and those they perceive to be dominant in their social worlds, prompted as necessary with key concepts in sexual health definition that have emerged since the first (now supplanted) definition adopted by the World Health Organisation in 1975. The results of this study will inform other targeted health interventions.
3. This study will address the question of how participants view sexual representation, both as targets of advertising and/or as consumers of pornography if appropriate and their perceptions of how this affects their sexual identity and practice.

Sexual health research is sensitive and requires a partnership approach with the communities in question. Specific collaborative arrangements including reference groups will be put in place to ensure the relevance of the questions being investigated, the suitability of the recruitment processes, the appropriateness of 'stakeholder' representatives and the comprehensive dissemination of findings. Importantly, the reference groups will be involved in discussing the final interpretation of the data, the weighing up of the benefits and harms to

determine the appropriate course of action with regard to whether mass drug distribution should go ahead.

Insights provided by this research program will facilitate better targeted health interventions. The specific component that addresses the acceptability of mass drug distribution will provide a direct answer as to whether this approach to STIs is acceptable and thus potentially feasible, or whether other approaches should be prioritised. The results of the mass drug dissemination component will inform future policy and funding decisions regarding targeted sexual health interventions for populations at high risk in Australia. These data will also provide important insights into the community concerns that will be relevant, though not necessarily directly applicable, to policy makers considering mass drug administration in other settings.

The strength of open-ended qualitative research as an empirical ethics methodology is that it can produce surprising results that could not be foreseen by researchers, thus it can change the parameters of how particular issues are understood, and open up new realms for research. Qualitative research into sexual health conducted in one population will not produce results that can be extrapolated directly to other settings, however, but it may provide relevant insights.

Priority

Addressing HIV and other communicable, sexually transmissible infections is a health priority, addressed in six successive national strategies on HIV, two on STIs, and three on STIs and blood borne viruses in Aboriginal and Torres Strait Islander people. Incidence and/or diagnosis of these infections is rising, however. HIV incidence has increased by 8.2% from 2010 with the majority of infections in men who have sex with men; diagnosis of chlamydia increased by 7% from 2010 and diagnosis of gonorrhoea increased by 45% since 2007. Infectious syphilis rates vary by state, but remain a problem both in men who have sex with men and Aboriginal populations (Kirby Institute 2012, 7-8). In the immediate Pacific region, women working in the sex or 'entertainment' industry who were not registered as sex workers had curable STI prevalence of 38% (Wi et al 2006).

These data show an unacceptable disease burden in particular populations that may have serious social effects. Both chlamydia and gonorrhoea if left untreated are implicated in causing pelvic inflammatory disease and infertility (Haggerty et al 2010), while untreated syphilis can cause a range of serious health problems, can be transmitted congenitally, an increases risk of HIV acquisition. HIV, while treatable, is a life-long infection that is life threatening without treatment, or with inadequate treatment.

Finding ways of intervening in cycles of infection that are acceptable and that enhance rather than diminish wellbeing is the ultimate sequelae of this research.

References

Adam, B.D. 2005. Constructing the neoliberal sexual actor: Responsibility and care of the self in the discourse of barebackers. *Culture, Health & Sexuality: An International Journal for Research, Intervention and Care* 7 (4): 33-346

Anderson, P.L., D. V. Glidden, A. Liu,et al. 2012. Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men. *Science Translational Medicine* 4 (151).

Baeten, J. M., D. Donnell, P. Ndase, et al. 2012. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine* 367 (5):399-410.

Bayer, R. AIDS prevention: sexual ethics and responsibility. *N Engl J Med.* 1996;3341540-1542.

Beauchamp, T.L., and J.F. Childress. 1994. Principles of Biomedical Ethics. Fourth ed. First published 1979. Oxford University Press: New York, NY.

Bollen, L. J. M., A. S. Anartati, G. Morineau, et al. 2010. Addressing the high prevalence of gonorrhoea and chlamydia among female sex workers in Indonesia: results of an enhanced, comprehensive intervention. *Sexually Transmitted Infections* 86 (1):61-65.

Borgerson, J. L. and Schroeder, J. E. 2005. Identity in Marketing Communications: An Ethics of Visual Representation. Marketing communication: new approaches, technologies, and styles, Allan J. Kimmel, ed., pp. 256-277, Oxford University Press. Available at SSRN: http://ssrn.com/abstract=969079

Carter, S. M., L. Rychetnik, B. Lloyd, et al. 2011. Evidence, Ethics, and Values: A Framework for Health Promotion. *American Journal of Public Health* 101 (3):465-472.

Dean, H.D. and K. A. Fenton. 2010. Addressing Social Determinants of Health in the Prevention and Control of HIV/AIDS, Viral Hepatitis, Sexually Transmitted Infections, and Tuberculosis. *Public Health Report* 125 (Supplement 4):1-5.

Edwards, W. M, and E.Coleman. 2004. Defining Sexual Health: A Descriptive Overview. *Archives of Sexual Behavior* 33 (3):189-195.

Grant, R. M., J.R. Lama, P. L. Anderson, et al. 2010. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *New England Journal of Medicine* 363 (27):2587-2599.

Grudzen, C.R, Kerndt, P.R. 2007. The Adult Film Industry: Time to Regulate? *PLoS Med* 4(6): e126. doi:10.1371/journal.pmed.0040126

Haggerty, C. L., et al. 2010. Risk of Sequelae after Chlamydia trachomatis Genital Infection in Women. *Journal of Infectious Diseases* **201**(Supplement 2): S134-S155.

Human Rights Watch. 2007. Social Justice Report 2007 Chapter 3: The Northern Territory 'Emergency Response' intervention. Available at: http://www.humanrights.gov.au/publications/social-justice-report-2007-chapter-3-northern-territory-emergency-response-intervention. Accessed 17 April 2013**.**

The Kirby Institute. 2012. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2012. The Kirby Institute, the University of New South Wales, Sydney, NSW 2052, p2.

Korenromp, E. L., C. Van Vliet, H. Grosskurth, et al. 2000. Model-based evaluation of single-round mass treatment of sexually transmitted diseases for HIV control in a rural African population. 2000. *AIDS* 14 , (5):573-593.

Luder, M-T, I. Pittet, A. Berchtold, et al. 2011. Associations Between Online Pornography and Sexual Behavior Among Adolescents: Myth or Reality? *Archives of Sexual Behavior* 40 (5):1027-1035.

Marrazzo, J., G Ramjee, G Nair, et al. 2013.Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine or vaginal tenofovir gel in the VOICE study (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 26LB, 2013.

Mayaud, P, and D. Mabey. 2004. Approaches to the control of sexually transmitted infections in developing countries: old problems and modern challenges. *Sexually Transmitted Infections* 80 (3):174-182.

Nussbaum, M. 2000. *Women and Human Development: The Capabilities Approach*, Cambridge University Press: Cambridge, MA.

Van Damme, L., A. Corneli, K. Ahmed, et al. 2012. Preexposure Prophylaxis for HIV Infection among African Women. *New England Journal of Medicine* 367 (5):411-422.

Wawer, M. J., N. K. Sewankambo, D. Serwadda, et al. 1999. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *The Lancet* 353 (9152):525-535.

Wi, T., E. R. Ramos, R. Steen, et al. 2006. STI declines among sex workers and clients following outreach, one time presumptive treatment, and regular screening of sex workers in the Philippines. *Sexually Transmitted Infections* 82 (5):386-391.

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I, ...[PRINT NAME], give consent to my participation in the research project

TITLE: *Standards of care in HIV biomedical prevention research in the developing world: the negotiation of benefits*
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3. I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher(s) or the University of Sydney now or in the future.

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7. I consent to: –

i) Audio-taping YES ☐ NO ☐

ii) Receiving Feedback YES ☐ NO ☐

If you answered YES to the "Receiving Feedback Question (iii)", please provide your details i.e. mailing address, email address.

Feedback Option

Address: _____

_____

Email: _____

Signed: .....

Name: .....

Date: .....

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If you agree to participate in this phase of the study, you will be asked to complete a questionnaire that will be emailed to you by the researchers. The questionnaire will ask questions regarding the process by which benefits to participants (standard of care, ancillary care and access to antiretrovirals) were determined in the study or studies in which you have been involved as a researcher, community liaison officer or ethical reviewer. The questionnaire will take about 15 minutes to complete.

All aspects of the study, including results, will be strictly confidential and only the investigators named above will have access to information on participants. A report of the study may be submitted for publication, but individual participants will not be identified in such a report. It is possible however that the identity of some participants may be inferred by readers of the subsequent thesis or other reports of this research. This is unlikely to be a problem for you, as the study is investigating the basis upon which decisions were made, while the outcomes of those decisions are already in the public domain.

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If you would like to know more at any stage, please feel free to contact Bridget Haire, PhD candidate, on +61 2 9036 3424, email bridget.haire@sydney.edu.au or Chris Jordens, Senior Lecturer, on +61 2 9036 3406, email: chris.jordens@sydney.edu.au

Survey link: http://www.surveymonkey.com/s/ethics_negotiation_of_benefits

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_____

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Signed: .....

Name: .....

Date: .....

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http://www.tandfonline.com/loi/uajb20

Back to Basics in Clinical Research Ethics

Bridget Haire [a]
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To link to this article: http://dx.doi.org/10.1080/15265160802654194

Back to Basics in Clinical Research Ethics

Bridget Haire, University of Sydney

The goal of restoring some uniformity to international guidelines about standards of care in research is a laudable one, but I remain unconvinced that Van der Graaf and Van Delden's (2009) proposed universal language will do the trick. The standard of care debate in the late 1990s was, I contend, more about the fundamental values that underlie clinical research than about how to choose the appropriate control arm in a randomized controlled trial, despite the obsessive focus that was devoted to the latter. Instead of rewording clauses (again) in an attempt to find a compromise between dyed -in-the-wool universalists and relativists, I suggest that a clear statement that the interests of research participants must *always* take precedence over the interests of science and society with regard to research design provide maximum protection with sufficient room for exceptional cases to be justified according to their merits.

In 2000, amidst great pressure to change ethical guidelines stipulating that the experimental therapies in clinical trials needed to be tested against the "best proven" therapeutic, preventive, or diagnostic method—an objective, clear standard—the Declaration of Helsinki changed to the similar but slightly more ambiguous wording, the "best current" method (Wolinsky 2006). This uneasy, and rather unclear, compromise was insufficient for the purposes of the relativist faction, who wanted ethical imprimatur to conduct research in the developing world to meet identified health needs, which may nevertheless fall below therapeutic standards in the developed world (Levine 1999).

Universalists opposed the weakening of the participants' protection that this entailed, arguing that it created a double standard, and most importantly subjugated the best interests of the research participants to those of science and society (Lurie and Wolfe 1997; Schüklenk 2004).

This ideological clash resulted in the reviewing and rewriting of a swathe of guidelines to include wording such as "the highest attainable," "the best available," "the best current," "a proven" or "an established effective treatment." The aim of these revisions was to provide decent subject protection but allow some regard for the context and the aims of research to influence study design (Mackin 2001).

Van de Graaf and van Delden's (2009) suggested replacement wording, which requires that participants in a control group should be assured of a treatment of "net clinical relevance for a specific condition that is under study for the population that the control group represents" is clear, precise and objective. I am unconvinced, however, that it offers any real advantage over the former Helsinki standard, the "best proven," and on that basis I suspect it will be rejected by anyone seeking to find leeway in research design.

Van der Graaf and van Delden (2009) begin with two questions. They ask whether a placebo is permissible where a proven or known effective therapy exists and whether it is acceptable to provide the control group in a developing country a level of care that is different or lower than the level that would be provided in the sponsoring country.

I suggest that the answers to these questions are already established: it is permissible to use a placebo despite established proven therapy when there is no increased risk or harm associated with it—that is, when the option of 'no treatment' is a valid therapeutic strategy. As to when it is acceptable to use a different standard in a developing country to that provided in the sponsoring country, the obvious answer is when the standard in the developing country is *better* for that population.

Solomon Benatar wrote in 1998, "It seems somewhat imperialistic to suggest that a drug regimen shown to be of value in some of the wealthiest countries in the world is necessarily the best proven regimen for some of the poorest" (221). In the context in which he wrote it, I disagree, in that he was apparently suggesting that the 076 regimen to reduce vertical HIV transmission might bring unforeseen harms—other than its rapacious cost—to developing world populations. In principle, however, he is right. 'Care' contains sociocultural and well as medical elements, and these aspects should certainly change in ways that are appropriate to context. The risk/benefit analyses for some procedures depend on the context in which care is delivered, with caesarean delivery being an obvious case-in-point—if a woman intends to have more children and cannot generally access hospital care, it may be a last resort only, whereas the recommendation may be different for a woman in other circumstances.

To illustrate the dilemmas of developing world research, Van der Graaf and van Delden (2009) cite the example of women in the contentious zidovudine trials not receiving the longer course because they would have been "forced... to abstain from breastfeeding" (35), which they describe as potentially "violating local [cultural] healthcare norms" (35). I agree that requiring women to artificially feed their infants in contexts where such feeding may be unsafe or unacceptable is highly problematic, but this example requires more analysis. Women in the PACTG 076 trial artificially fed their infants, and this method was a contributing factor

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to the low rate of HIV transmission postnatally, but it was not an element of the treatment protocol per se (Connor et al. 1994). There was no reason to suppose that a longer course of AZT prenatally, nor indeed as supplied to infants as post-exposure prophylaxis as stipulated in the 076 regimen, would be any riskier for either mother or baby in a breastfeeding context than the shorter zidovudine courses. Therefore I suggest that testing the 076 regimen against other, simpler regimens, in breastfeeding women would have been both scientifically and ethically valid.

We also need to be careful about invoking 'violation of cultural healthcare norms', given that *developing countries* is a phrase that involves an enormous range of social, cultural, economic and healthcare contexts, and that "culture" is a dynamic entity. Medicalized male circumcision may also 'violate healthcare norms' in some communities, but those norms can and arguably might need to change in response to HIV prevention imperatives. Obviously cultural change cannot be forced and needs to evolve from within rather than without, but it is possible—witness the widespread uptake of condoms in gay communities in the 1980s.

The goal of clinical research in the developing world must be to address health disparities—this is a point on which relativists and universalists agree. The difference, as illustrated in the debate over vertical transmission trial a decade ago, is how to achieve that.

The placebo-controlled short-course zidovudine trials were justified by some on the basis of putative outcomes to be enjoyed by later populations rather than the participants, and the harms that befell the participants—the higher than necessary rate of HIV transmission to infants—was rationalized as being not directly caused by the research, in that it would have occurred without the intervention. No direct benefits were granted to the women who had the misfortune to be randomized to placebo—neither they nor their infected infants were offered treatment, and there was no provision for ensuring that they had access to the proven regimen in any subsequent pregnancy. Indeed, the proven short-course zidovudine regimens were not widely implemented in the countries that ran the trials. While the reasons for this are complex and involve the development of cheaper and more effective nevirapine regimen**,** a consequentialist rationale demands to be judged by its consequences—and the short-course zidovudine failed to be implemented in the populations in which it was studied.

As Florencia Luna (2001) points out, the economic and political variables that determine access to therapies post-research are hard to control. The difficulty of achieving the expected benefits of research is in many respects as foreseeable and outcome as the harms that occur through not giving adequate care. How then can we justify conducting research that sacrifices the best interests of research participants—involving some deaths, and allowing other to go on with what Luna describes as the illness and handicaps produced by that research—to some uncertain end? The utilitarian spirit of this endeavor is in stark contrast to the guiding principle from the Declaration of Helsinki to place the interests of the subject above that of science and society.

To that end, I advocate that instead of quibbling over the wording of procedural clauses about specific trial design in guideline documents, that we re-embrace the protection of the research subject and the promotion of his or her best interests as being the principle obligation of the researcher. With that as the highest priority, "best proven" would once again become the default control arm standard, with variation only occurring when it was demonstrably in the subjects best interests—not the interests of the population more broadly, or the scientific endeavor—to do so. ■

REFERENCES

Benatar, S. R. 1998. Imperialism, research ethics and global health. *Journal of Medical Ethics* 24: 221–222.

Connor, E. M., Sperling, R. S., Gelber, R. et al. 1994. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *New England Journal of Medicine* 331(18): 1173–1180.

Levine, R. 1999. The need to revise the Declaration of Helsinki. *New England Journal of Medicine* 341(7): 531–534.

Luna, F. 2001. Is best proven a useless criterion? *Bioethics* 15 (4): 273–288.

Lurie, P., and Wolfe, S. M. 1997. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine* 337(12): 853–856.

Macklin, R. 2001. After Helsinki: Unresolved issues in international research, *Kennedy Institute of Ethics Journal* 11(1): 17–36.

Schüklenk, U. 2004. The standard of care debate: Against the myth of an "international consensus opinion." *Journal of Medical Ethics*: 30: 194–197.

Van der Graaf, R., and van Delden, J. J. 2009. What is the best standard for the standard of care in clinical research? *American Journal of Bioethics* 9(3): 35–43.

Wolinsky, H. 2006. The battle of Helsinki. *European Molecular Biology Organization* 7(7): 670–672.

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Treatment-as-Prevention Needs to Be Considered in the Just Allocation of HIV Drugs

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Treatment-as-Prevention Needs to Be Considered in the Just Allocation of HIV Drugs

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Since the beginning of the HIV epidemic, HIV advocates have resisted the competitive compartmentalisation of HIV programs into treatment versus prevention. Early resistance to HIV testing in gay male communities in the 1980s was predicated on the fact that in the absence of treatment, knowledge of asymptomatic HIV positive status could only be harmful (Bayer 1989). Once treatments were identified and made available, HIV testing became part of self-care, and the ethos that HIV research needed to address the needs of people living with the virus was enshrined in documents such as the Paris Declaration (1994). Nevertheless, polarizing of treatment versus prevention has persisted in some quarters.

Johansson and Norheim (2011) argue that the use of the Atkinson index may help to clarify the ethics of health policy choice. They demonstrate the strengths of this approach with four hypothetical cases studies where there are legitimate conflicts over prioritizing access to HIV resources: urban versus rural treatment access, HIV prevention versus treatment, treating adults compared with children, and treating more people compared with providing more expensive (complex) care.

In this commentary I consider how new research data that show that early HIV treatment has a significant treatment effect impact the treatment–prevention dichotomy, and I argue that there is a deceptive simplicity about the Atkinson index that may promote poor decision making, using the real-life examples of mother-to-child prevention programs, and the provision of more expensive second-line therapy to people with HIV who have developed drug resistance.

HPTN 052: TREATMENT AS PREVENTION

Paradoxically, new research results demonstrating the efficacy of HIV treatment as prevention may initially intensify health policy debates about pitting cost efficacy of HIV prevention against HIV treatment for those most in need—those with symptomatic disease.

HPTN 052 was a randomized controlled trial that showed that providing treatment to HIV-positive people prior to severe immune damage (at or above 350 CD4 cells[1]) was 96% effective in reducing HIV acquisition by their HIV-negative partners (Cohen et al. 2011). These results are welcome and provide an additional rationale for the scale-up of access to life-prolonging treatment in the resource-poor world.

At a time of shrinking HIV budgets on a global scale, however, it is inevitable that debates have begun as to whether the preventive effect of early treatment means that scarce treatment resources in developing countries will be diverted away from the sick toward expensive programs to test, and subsequently treat, people with asymptomatic HIV infection.

A person with a CD4 count of 350 or above is usually well, without symptoms of immune suppression, whereas in resource-poor countries, many people only seek HIV treatment when they are experiencing symptoms of HIV disease, usually when the CD4 cell count is well below 200. If treatment is a finite resource and there is an additional preventive benefit in treating a person with a higher CD4 count, that potentially deprives the sick person of life-prolonging treatment. In this schema the principle of providing treatment to those who would benefit most—the sickest—thus comes into conflict with the principle of health maximization, where both the person with HIV and his or her partners may benefit.

Denying treatment for the ill in order to prioritize those with the same condition at an asymptomatic stage, however, would endanger HIV programs. Though HIV is a stigmatized disease, effective antiretroviral therapy disaggregates HIV infection and death. Its impact is never as clear as when a sick person commences treatment and becomes well, the so-called "Lazarus" effect (Koenig et al. 2004). The prospect of treatment is what makes testing acceptable. Leaving the sick to die when they could access effective treatment would thus profoundly destabilize HIV programs.

I suggest that the slow uptake at operational level of the 2010 WHO Antiretroviral Treatment Guidelines attests to the primacy of treating the sick first. While the 2010 Guidelines raised the CD4 eligibility from 200 to 350 in response to cohort studies showing benefits of earlier treatment prior

1. CD4 cell counts provide a marker of immune function. They are progressively destroyed by HIV replication, and when the count drops to below 200, the risk of opportunistic infections rises exponentially. A person with an intact immune system would have in excess of 500 CD4 cells per cubic millimeter of blood.

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to the evidence provided by HPTN 052, those in medical need of treatment remained the priority.

But does this competition for treatment between the symptomatic person with HIV and the asymptomatic present a realistic picture of the challenges of resource distribution in the resource-poor world? I would argue that it does not. A meta-analysis of 28 trials looking at pre-antiretroviral care in Sub-Saharan Africa showed that more than two-thirds of those diagnosed as HIV positive but not yet treatment eligible were lost to care (Rosen and Fox 2011). Hence, the investment in identifying people with HIV is wasted if that does not lead to accessing treatment. If the diagnosis leads to treatment, however, the return on the investment in testing infrastructure is potentially twofold, both in sustaining the productive life of the healthy person with HIV, and in potentially protecting his or her partner from infection. The new data show that treating at a higher CD4 count does not have to occur at the expense of treating the sick to make economic, as well as moral, sense.

A further concern with the implementation of HPTN 052 into health policy is that people in stable serodiscordant relationships (where one is HIV positive and the other negative, as in the trial population) may be prioritized for early treatment, with its attendant benefits, over those who have less stable relationships or are single (Mayer 2011). This is clearly challenging from a health equity perspective. Thinking about the mechanism of the preventive effect of earlier treatment, it reduces infectivity. The HIV-negative sexual partner of an HIV-positive person taking treatment, who does not use other protection such as condoms, would benefit from that reduced infectivity. While it may be difficult to demonstrate this effect outside a stable relationship for logistical reasons, this should not alter the biological benefit to any partner, whether casual or regular.

CHEAP VERSUS EXPENSIVE INTERVENTIONS

Johannson and Norheim also apply the Atkinson index to the dilemma of whether to invest in low-cost drugs or high-cost drugs, in a scenario that is analogous to the resource allocation decisions about the level of treatment supplied to prevent mother-to-child transmission (PMTCT programs), and the supply of more expensive second-line HIV treatment for people failing[2] first-line treatment. Again Johannson and Norheim present these as ethical dilemmas related to potentially conflicting principles: health maximization, which favors quantitative outcomes, and health equity, which favors equitable distribution of health goods/equality in the age of death.

The trouble with both PMTCT programs and allocation of second-line therapy is that they are rather more complex than a choice between taking one pill (the cheap option) and taking two to achieve the same end.

Mother-to-child HIV transmission in high-income countries has reduced to below 2% through voluntary antenatal testing, provision of optimal combination antiretroviral therapy, and alternatives to breastfeeding. According to UNAIDS estimates, however, only an estimated 53% of pregnant women with HIV received any therapy, and 30% of these receive a cheap and efficient, but suboptimal, therapy—a single does of nevirapine (UNAIDS 2010, 78–80).

The simplicity and cost of the nevirapine regimen made it attractive from the perspective of health maximization when antiretroviral roll-out in low income countries was in its infancy. A decade or so on, the shortcomings are stark: Drug resistance can develop in the mother from a single dose, which then dramatically reduces its effectiveness for subsequent pregnancies; drug resistance to nevirapine impacts on any subsequent antiretroviral therapy provided for the mother's own health, and nevirapine is less effective in preventing HIV transmission than a complex regimen in the first place (Johnson et al 2005). Mothers with drug-resistant virus are more likely to fail first-line therapy, meaning either that they require more expensive second-line therapy, or that they die, and potentially leave orphans who are less likely to survive without a mother.

Similarly, constraining the use of second-line therapy in order to maximize health (supplying more first line therapy to more people) creates more complex health issues in the foreseeable future. Second-line HIV therapy is designed to be efficacious in people who have resistance to, or intolerance of, first-line therapy. Failure to switch a patient onto second-line therapy both seriously jeopardizes her health (squandering the initial investment in first-line therapy) and promotes the development of drug-resistant HIV, which is transmissible and has the potential to render first-line therapy ineffective.

Treatment-as-prevention, PMTCT programs, and first- and second-line HIV therapy raise complex issues for health policy in the context of limited resources, and indeed, I have not even touched on pertinent implementation issues. There is dynamic interplay among donors, governments, and communities about what is an acceptable minimum standard, with universal access being the stated goal. In the meantime, it is necessary to be transparent about the rationale for prioritization, and that discussion needs to take place with a full understanding of both the social and the public health consequences of inequitable or suboptimal programs. ■

2. "Failing" meaning that the first-line drugs are not suppressing viremia.

REFERENCES

Bayer, R. 1989. Testing, reporting and notifying; The politics of identification. In *Private acts, social consequences*, 101–136. New York: The Free Press.

Cohen, M. S., Y. Q. Chen, M. McCauley, et al. 2011. Prevention of HIV-1 infection with early antiretroviral therapy. *New England Journal of Medicine*, in press.

Johansson, K. A., and O. F. Norheim. 2011. Problems with prioritization: Exploring ethical solutions to inequalities in HIV care. *American Journal of Bioethics* 11(12): 32–40.

Johnson, J. A., J.-F. Li, L. Morris, et al. 2005. Emergence of drug-resistant HIV-1 after intrapartum administration of single-dose nevirapine is substantially underestimated. *Journal of Infectious Diseases* 192(1): 16–23.

Koenig, S. P., F. Léandre, and P. E. Farmer. 2004. Scaling-up HIV treatment programmes in resource-limited settings: The rural Haiti experience. *AIDS* 18(suppl. 3): S21–S25.

Mayer, K. H. 2011. Antiretrovirals for HIV prevention: Translating promise into praxis. *Lancet* 378(9787): 206–208.

Paris AIDS Summit. 1994. *Paris declaration*. Available at: http://www.positivelivingbc.org/files/resources/paris-declaration-1994.pdf (accessed August 5, 2011).

Rosen, S., and M. P. Fox. 2011. Retention in HIV care between testing and treatment in sub-Saharan Africa: A systematic review. *PLoS Medicine* 8(7): e1001056.

UNAIDS. 2010. Joint United Nations Programme on HIV/AIDS. Global report: Report on the AIDS epidemic 2010. Available at: http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf (accessed August 5, 2011).

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The seventh (and last?) International Microbicides Conference: from discovery to delivery

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Abstract. The most recent estimates indicate that in 2011, 34 million people were living with HIV, the majority in sub-Saharan Africa. Even though the estimated number of new infections is decreasing, there remains an urgent need for new prevention technologies, particularly those controlled by women and men who have receptive sex. Microbicides are products designed to be applied vaginally or rectally to prevent acquisition of HIV and other sexually transmissible infections and, as such, provide a great hope for female-controlled HIV prevention. Oral prevention drugs are a more recent development that also has great potential. The field changed radically in 2010–2011 with the first trials demonstrating effectiveness of a microbicide and oral prevention drugs. The seventh biannual Microbicides conference, which took place in Sydney, Australia, in April 2012, was the first conference in this series since these new results and represented a transition from the discovery phase of research to considerations of implementation. Researchers, advocates, community representatives, funders and the media came together over 3 days to talk about the realities of implementation, particularly in regard to challenges in adherence and funding, and also examined early findings for new prevention technologies. This report of the 2012 International Microbicides Conference provides a summary of recent developments and ongoing challenges in the field of microbicides research.

Additional keywords: female-controlled prevention, HIV, oral prevention drugs, pre-exposure prophylaxis.

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Introduction

According to the latest estimates from UNAIDS, there were 2.5 million new HIV infections in 2011, representing a decrease of 20% compared with 2001.[1] Nevertheless, the total number of people living with HIV worldwide is estimated to have increased to 34 million in 2011,[1] reflecting both the new infections and the reduction in deaths due to improved access to antiretroviral therapy.[1] Globally, the proportion of women infected has remained stable at 50%, but they represent the majority of infections in sub-Saharan Africa (59%) and the Caribbean (53%).[1] The recent policy emphasis on the use of treatment as prevention, driven largely by the findings of the HIV Prevention Trials Network (HPTN) 052 trial released in 2011, will require a massive expansion of diagnosis and treatment services, and will not protect the partners of those whose HIV infection has not yet been diagnosed and controlled by treatment.

In April 2012, the seventh conference in the biennial Microbicides series, the 2012 International Microbicides Conference (M2012), was held in Sydney, Australia. Its objective was to consider new findings and their implications in the field of microbicides and oral pre-exposure prophylaxis (PrEP) for HIV prevention. With support from the United States National Institutes of Health Office of AIDS Research, the Bill and Melinda Gates Foundation and other agencies, the conference attracted over 600 delegates from around the world, including some 300 scholarship recipients, predominantly from sub-Saharan Africa, the region most affected by the HIV epidemic.

The conference theme 'From discovery to delivery' reflected the evolving nature of the fields of microbicides and oral PrEP. Striking new developments since the previous conference in the series (Microbicides 2010 in Pittsburgh) provided renewed momentum after some earlier trial disappointments (see Fig. 1 for a summary of recent HIV prevention trials). In the second half of 2010, the Centre for the AIDS Programme of Research In South Africa (CAPRISA) 004 trial showed that tenofovir gel reduced the risk of infection in women using the product, and the Preexposure Prophylaxis Initiative (iPREX) trial demonstrated prevention success for daily oral tenofovir and emtricitabine in gay men. During 2011, two new trials,

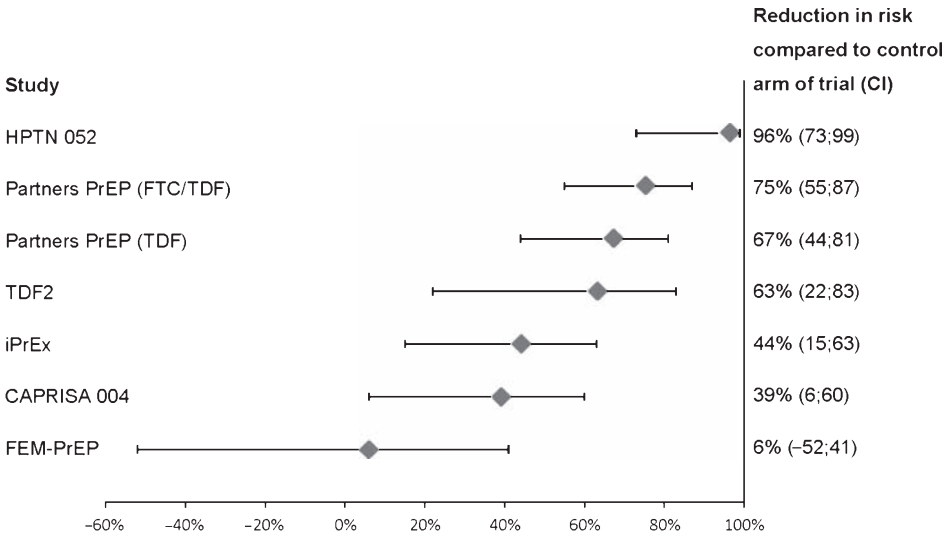

Fig. 1. Effect sizes and 95% confidence intervals from recent HIV prevention trials.[39–41] HPTN 052, treatment as prevention in discordant couples; Partners PrEP, oral Truvada or Viread in discordant heterosexual couples; TDF2, oral Truvada in high-risk heterosexuals; iPrEX, oral Truvada in men who have sex with men; CAPRISA 004, topical tenofovir gel; FEM-PrEP, oral Truvada in high-risk women.

Partners PrEP and Botwsana TDF/FTC Oral HIV Prophylaxis Trial (TDF2), also found in favour of oral chemoprevention as a prevention strategy for both heterosexual men and women, although two other trials (FEM-PrEP and VOICE) failed to find benefit for women, and a trial of tenofovir gel in one arm of the VOICE study, using a daily dosing strategy that differed from the one used in CAPRISA 004, also found no protection. Along with the HPTN 052 trial, which showed that effective treatment of people with HIV infection decreased their infectiousness by over 95%, and the existing evidence for male circumcision as a means of protecting men, HIV prevention is now a complex field of biomedical, behavioural and structural strategies, bringing with them the challenges of delivery in a wide variety of settings and the difficult choices that will need to be made when allocating limited resources. The challenges of discovery also continue, as the currently available agents are far from fully effective, and continuing development is needed to improve the potency of prevention products at the same time as ensuring that they are safe and acceptable for all those who stand to benefit.

M2012 explored issues of access to prevention technologies, adherence in clinical trials, multipurpose prevention technologies, the ethical challenges of future prevention trials and new methods of preventing the rectal transmission of HIV. We report here on the proceedings of M2012, with respect to discussions and outcomes under the four theme areas of basic science, community and advocacy, clinical science, and social and behavioural science.

The biology of mucosal transmission

With adherence emerging as a key issue (see below), the basic science focus at M2012 was largely in the area of pharmacodynamics. Connie Celum from the University of Washington presented data from Microbicide Trials Network (MTN)-001, which examined the pharmacokinetic and pharmacodynamics of oral tenofovir in women, revealing that there were far lower levels of the drug in the vagina compared with the rectum.[2] Complementary findings in pigtailed macaques were presented by Walid Heneine from the Centers from Disease Control and Prevention, indicating the utility of this model for evaluating the pharmacology and efficacy of PrEP.[3] Several presentations considered the biological basis for the apparent differences in PrEP efficacy observed in women.

Salim Abdool Karim from the University of KwaZulu-Natal opened the conference with an inspirational overview of the trials and tribulations of the microbicide field over the past 20 years. He outlined lessons learned in the quest to develop an efficacious microbicide, culminating in the success of the CAPRISA 004 trial.[4] The key messages included the need for diversity in product development and for genuine community partnerships in trial planning and implementation. New data from CAPRISA 004 showed that, irrespective of tenofovir use, women who acquired HIV had significantly higher levels of systemic innate immune activation before HIV infection compared with women who remained free of infection.[4] Furthermore, the protective effect of tenofovir gel was weaker in women who were found to have genital inflammation, as detected by raised cytokine levels following gel use.

Betsy Herold from the Albert Einstein College of Medicine showed how the design of effective PrEP can be informed by an understanding of the biology of HIV transmission.[5,6] She emphasised that HIV transmission via sex is an inefficient process due to physical barriers, mucus, innate antiviral factors and products produced by healthy microbes present in the female genital tract. However, the balance can be tipped towards promotion of HIV infection, even in the presence of an antiviral drug, by several factors, including the act of sex, the presence of semen, high viral load in the partner, the virulence of the virus, sex hormones and immune activation, such as might

arise through a sexually transmissible infection or bacterial vaginosis. A greater understanding of the basic biology of HIV transmission in genital tissue is required to inform PrEP development and formulation, and to develop better preclinical models for predicting PrEP's safety and efficacy *in vivo*.

A recurring theme at the conference was the role of inflammation in enhancing HIV infection in the female genital tract. In a symposium dedicated to this topic, Jeanne Marrazzo from the University of Washington, Alan Landay from Rush University Medical Center and Richard Cone from Johns Hopkins University reviewed our current knowledge of the vaginal microbiome in healthy women of reproductive age, the microbiome in women with bacterial vaginosis, and changes in the microbiome that could either enhance or diminish HIV acquisition.[7–9] Marrazzo reported from a prospective cohort study conducted in East Africa demonstrating a three-fold increased risk of female-to-male HIV transmission among men whose female partners had bacterial vaginosis compared with women with normal vaginal flora.[7] Cone presented data on lactic acid produced by *Lactobacilli* sp., which is responsible for acidifying the female vagina as an antimicrobial defence mechanism.[9] Steven Zeichner from George Washington University showed that the failed microbicide candidates nonoxynol-9 and cellulose sulfate mediate changes in the vaginal microbiota towards nonlactobacilli-containing communities.[10] Intriguingly, these microbial communities are not generally associated with the elevated Nugent scores that are conventionally used to diagnose bacterial vaginosis, suggesting that this scoring system might be inadequate for assessing the safety of candidate microbicides and that a DNA method of sequencing (pyrosequencing) may be a preferable means of defining the vaginal microbiota (i.e. bacterial communities).

Helen Rees from the Wits Reproductive Health & HIV Institute dissected the recent controversy surrounding the role of progestogen-only injectable contraceptives in the risk of HIV acquisition.[11] Analysis of the studies as a whole indicates that although there is some indication of increased risk, the data were not sufficiently conclusive to change current guidelines that permit their use. On a related topic, there was considerable enthusiasm for 'multipurpose prevention technology' as reviewed by Joseph Romano from the NWJ Group.[12,13] Multipurpose prevention technologies can take several forms including drugs or drug combinations that target more than one sexually transmissible infection such as HIV and the herpes simplex virus, or a device such as a diaphragm to prevent pregnancy that also releases an antiviral and multi-indication vaccines. Romano described proposed multipurpose prevention technology products consistent with the 'target product profile' that are under development and acknowledged that multipurpose prevention technologies will present new challenges to regulators, researchers and communities.

The role of community and advocacy

The promise of microbicides and PrEP demonstrated by the recent successful trials, together with the caution raised by the negative findings from others, provided a context for implementing questions of great concern to communities, such as which populations will really benefit from new prevention technologies and how people will incorporate them into their sexual practices.

Dean Murphy from the Australian Federation of AIDS Organisations presented results from PrEPARE, an online survey of Australian HIV-positive and HIV-negative men intended to gather information pertinent to PrEP implementation.[14] The study found that two-thirds of all anal sex was unplanned, suggesting that event-based dosing may not be effective, and that intermittent plus post-sex dosing strategies may be a more achievable strategy in this population.

Sexual practice within microbicide trials and the cultural framing of the investigational product was examined by researchers from the Microbicides Development Programme (MDP) 301 study in several presentations. Shelley Lees from the London School of Hygiene and Tropical Medicine reported on qualitative research conducted at the Mwanza, Tanzania, site of the MDP 301 clinical trial with women working in the local hospitality industry who may engage in transactional sex.[15] Lees found that although these women were aware of their vulnerability to HIV, their discussions of sexuality were more complex than a focus on risk. For them, 'traditional' sexuality represented respect combined with men's sexual control of women, whereas 'modern' sexuality represented disrespect and HIV risk, but also involved a greater choice for women in terms of love, intimacy and pleasure. Lees argued that HIV prevention research needs to move beyond risk to understand women's sexual lives more broadly, in order to understand how they may adopt new HIV prevention technology.

Mitzy Gafos from the Medical Research Council conducted qualitative research with MDP 301 participants in a predominately rural area of KwaZulu-Natal, South Africa. She explored the meanings of the microbicide gel with reference to the traditional concept of 'love medicines,'[16] which are perceived as a way for women to control the course of a relationship, at the same time as being highly stigmatised within these communities. Gafos' analysis suggested that women made a distinction between microbicide gels and the love medicines to avoid the stigma and warned researchers against invoking such traditional practices to 'sell' microbicides.

The criminalisation of both HIV transmission and homosexuality in various African countries was an important focal point of M2012, and was explored in a symposium with speakers from South Africa, Kenya and Australia. Brian Kanyemba of the Desmond Tutu HIV Foundation in South Africa told the conference that homosexuality is criminalised in 38 African countries, undermining the effectiveness of the HIV response.[17] Kanyemba contrasted HIV prevention in South Africa, where same-sex marriage is recognised and gay men and lesbians protected by a Bill of Rights, with countries such as Zimbabwe, Zambia, Malawi, Uganda and Kenya, where there are legal penalties, and noted the resulting diversion of funds, human rights abuses and disengagement from prevention services by this vulnerable population. He also identified criminalisation of homosexuality as a major barrier to effective uptake of biomedical prevention strategies such as microbicides and PrEP.

A symposium on the HIV prevention needs of HIV-positive women reflected the concern about the possibility of women

being excluded from prevention discoveries. Discussions focussed on the development of new prevention tools for HIV-positive women, access to existing tools and the other issues that impact on HIV-positive women's ability to protect themselves, their partners and their children. Technologies that might be beneficial, such as therapeutic vaccines and nonantiretroviral-based microbicides, were described.[18,19] Jane Bruning from Positive Women Inc. (New Zealand) outlined the various forms of female condom and the different properties they offer,[20] leading to a lively discussion of the lack of access to this under-used female-controlled technology and the need for a global strategic commitment. Lucy Ghati from the National Empowerment Network of People Living with HIV/AIDS in Kenya provoked impassioned debate about the impacts of treatment-as-prevention on HIV-positive women,[21] with some arguing it would improve access while other saying that it increased the burden of responsibility and had coercive potential.

A rectal microbicides symposium blended science with advocacy, with Ian McGowan from the University of Pittsburgh School of Medicine outlining the past and anticipated research trajectory of these agents,[22] and advocates Kadiri Audu from the International Center for Advocacy on Right to Health and Jim Pickett from the AIDS Foundation, Chicago, discussing the advocacy agenda.[23,24] An understanding of anal health and anal sex practices was recognised as being an essential underpinning for development in this area.

Ethical challenges in taking prevention research forward

The ethics of HIV prevention research was a prominent topic at M2012. Key ethical challenges identified were the standard of prevention to be applied in new trials, now that there were products available that had preventive efficacy, and post-trial access to effective products. In the standard of prevention symposium, Ruth Macklin from Albert Einstein College of Medicine, Jeremy Sugarman from Johns Hopkins Berman Institute of Bioethics and Catherine Hankins from UNAIDS outlined the differences in current ethical guidelines on this issue.[25–27] Morenike Ukpong from Obafemi Awolowo University in Nigeria advocated for effective community participation and described the pitfalls of consultation that happens too late in the development of a protocol in communities that have low research literacy and limited capacity to contribute meaningfully.[28] In the post-trial access symposium, Ruth Macklin outlined the rationale for post-trial access, arguing that trial participants have a particular moral claim to products they helped to test. The implementation difficulties of ensuring post-trial access were discussed at length with panellists and the audience, with Salim Abdool Karim from CAPRISA explaining the regulatory issues that had held up access to tenofovir gel for trial participants after the successful conclusion of CAPRISA 004.[4]

Adherence is the key to effectiveness

Understanding adherence in HIV prevention trials was a recurring theme of M2012, discussed at several plenary sessions, symposia and proffered paper sessions. In a symposium session titled 'Making sense of the PrEP Trial Results', Amy Corneli from FHI 360 noted that the apparent lack of an effect may be entirely due to adherence.[29] Douglas Taylor also from FHI 360 outlined the limitations of traditional measures of adherence, such as self-report and pill or applicator count data and suggested that antiretroviral-based products may allow for more objective measures of adherence.[30] Corneli provided information on methods that had been used to support adherence in recent trials.[29] Both Corneli and Richard Hayes (London School of Hygiene and Tropical Medicine), in his plenary session,[31] emphasised the need for standardised measures of adherence to aid comparison of findings across trials.

A symposium session addressed novel approaches to measuring adherence. Richard Cone described the Medication Event Monitoring System, which is widely used in therapeutic research, and four novel methods to test for vaginal secretions on applicators.[32] Although the use of ultraviolet light proved easy for participants, fast and reliable for record keeping and analysis, and allowed for rapid identification of poorly adherent participants, it was not a sufficient measure in isolation. Ariane van der Straten from RTI International, noted that improved adherence measurement requires a combination of self-report, electronic monitoring devices, biomarkers and other objective measures such as applicator tests and directly observed therapy.[33] The overall message was that more studies need to be conducted to validate novel measures of adherence, even if there is currently no gold standard.

New results from early phase trials

Several presentations focussed on recent Phase I and II microbicide trials. Ian McGowan reported on MTN-007, a Phase I randomised, double-blind, placebo-controlled rectal safety and acceptability study of tenofovir 1% gel.[34] Participants were randomised 1 : 1 : 1 : 1 to receive a reduced glycerin tenofovir 1% gel, a hydoxyethylcellulose placebo gel, a 2% nonoxynol-9 gel or no treatment. The study concluded that the reduced glycerin formula of 1% tenofovir was safe and well tolerated.

Nicola Richardson-Harman from Alpha StatConsult LLC described the dose–response relationship in RMP-01, the first randomised, double-blind, placebo-controlled Phase I antiretroviral rectal microbicide trial.[35] A vaginal gel, UC781, was applied topically (0.1% *v.* 0.25% *v.* placebo; 1 : 1 : 1). Their analysis demonstrated that tissue UC781 levels and *ex vivo* infectibility data enable dose–response correlations. The study was important in that it demonstrated the feasibility and allowed comparisons of microbicide efficacy between drugs, compartments and application methods, without the dependence on baseline infectivity data or frequency exposure.[35]

Recognition of outstanding achievement

Two conference awards were presented on the closing day of M2012. Anna Forbes was awarded the Omololu Falobi Award for Excellence in HIV Prevention Research Community Advocacy for her significant contributions over a long career

dedicated to fostering civil society engagement in women's rights, and HIV care, treatment and prevention. Lut Van Damme from FHI 360 and Gita Ramjee from the Medical Research Council, who have had major roles in many of the key microbicide trials, were honoured with the conference Lifetime Achievement award. In his nominating speech, 2010 recipient Henry Gabelnick from CONRAD spoke of their enormous contribution and determination in the face of the many obstacles that clinical trials must deal with.

The future of HIV prevention research

Several sessions throughout M2012 provided insight into the challenges the field of microbicide research faces in conducting trials. Angela Crook from the Medical Research Council Clinical Trials Unit (proffered paper session)[36] and Richard Hayes (plenary session)[31] both noted that it will be increasingly difficult to justify a placebo arm in trials, with products like tenofovir gel providing promise for HIV prevention. Without a placebo arm, a much larger sample size will be required to reach adequate power, which has significant implications for resourcing. Crook used the example of comparing a single-dose tenofovir regimen to a two-dose before-and-after regimen to demonstrate the feasibility of noninferiority microbicide trials despite the large sample size required.[36]

It is apparent that the field of HIV prevention and prevention research is going to face serious shortfalls in funding in the coming years. Debrework Zewdie from The Global Fund to Fight AIDS, Tuberculosis and Malaria addressed this issue in the closing plenary session.[37] The key message was that the field of microbicides needs to look to innovative financing and the private sector. She also pointed out the significant delay to implementation from the results of male circumcision and prevention of mother-to-child transmission trials, and challenged the microbicide community to be prepared for faster realisation in the future. This reinforced Milly Katana's plenary session, where she urged consideration of issues of access now, rather than waiting until trial results were released.[38]

The future of HIV prevention conferences

The Conference concluded with a joint presentation by Gina Brown from the US National Institutes of Health Office of AIDS Research and Stephen Becker from the Bill and Melinda Gates Foundation, representing the two bodies that have provided most of funding for the Microbicides series of conferences over the past 12 years. They announced the intention of the funders to bring together vaccines, microbicides, oral PrEP and other HIV prevention modalities in a new conference series, effectively drawing the Microbicides series to a close. This new biennial global HIV prevention conference series is likely to commence in 2014. Discussion following their presentation emphasised the need to maintain a strong interdisciplinary focus, particularly involving community, advocacy and social science, to ensure that the unique flavour of the Microbicides series was maintained.

References

1 UNAIDS. World AIDS Day report 2012. Geneva: UNAIDS; 2012.
2 Celum C. State of the evidence from efficacy trials: What we know and what we still need to know. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
3 Heneine W. Tenofovir gel in the monkey model and other PK findings on the impact of menstrual cycle on vaginal drug absorption and bidirectional dosing. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
4 Abdool Karim S. CAPRISA 004 two years on: what were the lessons, what are the implications? 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
5 Herold B. The biology of HIV transmission: implications for the design of effective PrEP. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
6 Herold B. Antiviral activity in cervicovaginal lavage (CVL) as a biomarker of the potential efficacy of topical and oral pre-exposure prophylaxis (PrEP): results from the MTN 001. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
7 Marrazzo J. The vaginal microbiome and BV (clinical/diagnosis/biofilms). 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
8 Landay A. HIV, BV and the innate immune response. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
9 O'Hanlon DE, Tachedjian G, Moench TR, Cone R. When lactobacilli dominate (Nugent score 0–3) they inactivate HIV and BV bacteria with lactic acid. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
10 Ravel J, Gajer P, Fu L, Koenig S, Sakamoto J, Motsinger-Reif A. *et al*. Effects of HIV vaginal microbicides on the vaginal microbiota as determined by pyrosequencing of 16S rRNA genes. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
11 Rees H. HIV and contraception. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
12 Romano J. The barriers and incentives in the pathway to developing a usable new technology for HIV prevention. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
13 Stewart K, Young Holt B, Romano J, Harrison P, Turpin J, Kerrigan M, *et al*. Multipurpose prevention technologies (MPTs) for sexual and reproductive health: integrating basic and behavioral science throughout the critical path. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
14 Murphy DA, De Wit JBF, Holt M, Callander D, Ellard J, Rosengarten M, *et al*. Only a minority of sex is planned among gay men in Australia: findings from the PrEPARE project. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
15 Lees S, Sufiani A, Celestine V, Hilali E, Kiro K, and the MDP trial team. Microbicides: addressing Tanzanian women's broader concerns with sexuality. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.

16 Gafos M. 'The things we do for love': love medicines and microbicides in a predominantly rural area of KwaZulu-Natal, South Africa. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
17 Kanyemba B. Contextualising pre-exposure prophylaxis for the realities of HIV prevention and care in South Africa: outcomes from a community-based advocacy project. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
18 Forbes A. Status report: where are we on development of new tools relevant to women with HIV? Non-ARV based microbicides. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
19 Patten S. Status report: where are we on the development of new tools relevant to women with HIV? Therapeutic vaccines. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
20 Bruning J. Female condom. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
21 Ghati L. Advocacy and structural issues overall. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
22 McGowan I. Rectal microbicides development – where have we been and where are we going? 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
23 Audu K. Rectal microbicide advocacy in Africa. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
24 Pickett J. Around the world with IRMA – global rectal microbicide advocacy priorities, opportunities and challenges. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
25 Hankins C. Standard of prevention in the UNAIDS/WHO guidelines. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
26 Macklin R. Ethical principles for addressing post-trial access to new HIV prevention options for women. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
27 Sugarman J. Ethical obligations and aspirations regarding prevention and care in HIV prevention research. International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
28 Ukpong M. A community advocate's perspective on the standard of care issue. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
29 Corneli A. Motivators of adherence in clinical trials. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
30 Taylor D. Asking about and measuring adherence. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
31 Hayes R. The future of HIV prevention trials in HIV. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
32 Moench TR, O'Hanlon DE, Cone R. MEMS monitoring and UV inspection of applicators as a quantitative assessment of adherence. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
33 Van Der Straten A. Self reports, electronic monitoring and biomarkers: how best to integrate these tools to explain adherence? 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
34 McGowan I, Hoesley M, Cranston R, Andrews P, Janocko L, Dai J, *et al*. MTN:007 a Phase 1 randomised, double blind, placebo controlled rectal safety and acceptability study of tenofovir 1% gel. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
35 Richardson-Harman N, Elliott J, Janocko L, Cumberland W, Zhou Y, McCormick T, *et al*. Dose–response relationship between rectal tissue levels of rectally-applied UC781 microbicide gel and reduction of *ex vivo* HIV infectibility of biopsies from *in vivo* exposed rectal tissue from the Phase 1 trial RMP-01. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
36 Crook A, McCormack S, Nunn A. Designing microbicide trials without a placebo. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
37 Zewdie D. Who pays? Global resourcing for new HIV prevention technology. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
38 Katana M. Making access a reality for all those in need. 2012 International Microbicides Conference, 15–18 April, Sydney, Australia. Sydney: Australasian Society for HIV Medicine; 2012.
39 Baeten J, Celum C. Oral antiretroviral chemoprophylaxis: current status. *Current opinion in HIV and AIDS* 2012; 7(6): 514–19. doi:10.1097/COH.0b013e3283582d30
40 Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, *et al*. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; 365(6): 493–505. doi:10.1056/NEJMoa1105243
41 Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, *et al*. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010; 329(5996): 1168–74. doi:10.1126/science.1193748

Investigator/research staff questionnaire (supplanted draft)

1. How many phase IIB or Phase III HIV prevention trials have you been involved in? Please list.

	Response Count
	3
answered question	**3**
skipped question	**7**

2. Which HIV prevention intervention/s have you been involved in testing?

	Response Percent	Response Count
PrEP	40.0%	4
HIV vaccine	20.0%	2
Microbicide	**80.0%**	**8**
PrEP/microbicide	0.0%	0
Treatment-as-prevention	10.0%	1
Other (please specify)	10.0%	1
answered question		**10**
skipped question		**0**

3. What was your role in the trial or trials?

	Response Percent	Response Count
Principal investigator	**80.0%**	**8**
Senior member of research team	40.0%	4
Community liaison officer	0.0%	0
Other (please specify)		1
answered question		**10**
skipped question		**0**

4. What research ethics guidelines were used?

	Response Percent	Response Count
National guidelines of host country	33.3%	3
CIOMS (Council for International Organisations of Medical Sciences)	33.3%	3
Declaration of Helsinki	**88.9%**	**8**
UNAIDS	33.3%	3
Nuffield Council on Bioethics	11.1%	1
NBAC (National Bioethics Advisory Commission)	0.0%	0
HPTN	11.1%	1
Other (please specify)	22.2%	2
answered question		**9**
skipped question		**1**

5. Did your research strictly adhere to the research ethics guidelines used?

		Response Percent	Response Count
Yes, with no likely deviation		**80.0%**	**8**
Yes, but compliance with the provision to ensure access to a proven product uncertain		30.0%	3
No, some deviations have been negotiated		0.0%	0
		Comment (optional)	1
		answered question	**10**
		skipped question	**0**

6. Where did you obtain ethics approval for your trial?

		Response Percent	Response Count
In the host country		10.0%	1
In the sponsoring country		0.0%	0
In both host and sponsoring countries		**90.0%**	**9**
		Please name ethics committees used	6
		answered question	**10**
		skipped question	**0**

7. Did you discuss distribution of research benefits with local communities?

		Response Percent	Response Count
No		10.0%	1
Yes, in planning stages		20.0%	2
Yes, in recruitment stages		20.0%	2
Yes, in planning and recruitment stages		**50.0%**	**5**
		Comment (optional)	1
		answered question	**10**
		skipped question	**0**

8. Is antiretroviral therapy provided to seroconverters?

		Response Percent	Response Count
No		25.0%	2
Not sure		0.0%	0
Yes, through government programs		**50.0%**	**4**
Yes, through international donor programs		12.5%	1
Yes, directly linked to the research program		12.5%	1
		(please list any special provisions that assist in antiretroviral access)	6
		answered question	**8**
		skipped question	**2**

9. Is antiretroviral therapy provided to HIV positive volunteers who are screened out?

	Response Percent	Response Count
No	**33.3%**	**3**
Yes, through government programs	**33.3%**	**3**
Yes, through international donor programs	22.2%	2
Yes, directly linked to the research program	11.1%	1
(please list any special provisions that assist in antiretroviral access)		6
answered question		**9**
skipped question		**1**

10. Does the trial offer ancillary medical benefits to participants?

	Response Percent	Response Count
No	20.0%	2
Yes, sufficient to ensure smooth running of the research	30.0%	3
Yes, to treat conditions uncovered through the research processes	10.0%	1
Yes, to the degree possible on the basis of need	**40.0%**	**4**
answered question		**10**
skipped question		**0**

11. Which benefits does the trial offer participants?

	Response Percent	Response Count
Male condoms (limited numbers)	10.0%	1
Male condoms (free, unlimited)	90.0%	9
Female condoms (limited numbers)	10.0%	1
Female condoms (free, unlimited numbers)	40.0%	4
STI testing/treatment	**100.0%**	**10**
Hormonal contraception (limited options)	10.0%	1
Hormonal contraception (comprehensive options)	30.0%	3
HPV vaccination	0.0%	0
Hepatitis B vaccination	10.0%	1
Male circumcision for participants/partners	0.0%	0
Cervical screening	70.0%	7
Treatment of cervical dysplasia	30.0%	3
Referrals to local services for non-trial related illness/injury	80.0%	8
	Comment (optional)	6
	answered question	**10**
	skipped question	**0**

12. Are benefits provided to partners or families of participants?

		Response Percent	Response Count
No		**62.5%**	**5**
Yes		37.5%	3
		Comment (optional)	4
		answered question	**8**
		skipped question	**2**

13. Does your trial contribute infrastructure to the host country?

		Response Percent	Response Count
No		22.2%	2
Yes (please specify)		**77.8%**	**7**
		answered question	**9**
		skipped question	**1**

14. Will this infrastructure contribute to meeting health needs or research capacity of the community post-trial?

		Response Percent	Response Count
No		22.2%	2
Yes (please specify)		**77.8%**	**7**
		answered question	**9**
		skipped question	**1**

15. Does the trial sponsor limit benefits that are made available to participants?

		Response Percent	Response Count
No		42.9%	3
Yes		**57.1%**	**4**
		Comment (optional)	5
		answered question	**7**
		skipped question	**3**

16. Are you satisfied with the benefits that the trial provides to participants?

		Response Percent	Response Count
No		0.0%	0
Yes		**75.0%**	**6**
Partially		25.0%	2
Unsure		0.0%	0
		Comment (optional)	1
		answered question	**8**
		skipped question	**2**

Investigator/research staff questionnaire (final)

1. How many phase IIB or phase III biomedical HIV prevention trials have you been involved in? (Please include trials you are CURRENTLY involved in as well as those completed.)

	Response Percent	Response Count
One	29.4%	5
More than one	**70.6%**	**12**
	answered question	**17**
	skipped question	**0**

2. Which HIV prevention intervention have you been involved in testing?

	Response Percent	Response Count
PrEP	20.0%	1
HIV vaccine	0.0%	0
Male circumcision	**40.0%**	**2**
Microbicide	**40.0%**	**2**
PrEP/microbicide	0.0%	0
Treatment-as-prevention	0.0%	0
STI treatment as HIV prevention	0.0%	0
Diaphragm	0.0%	0
	Please specify approximate start date of trial	2
	answered question	**5**
	skipped question	**12**

3. What was your role in the trial or trials?

	Response Percent	Response Count
Principal investigator	**100.0%**	**5**
Senior member of research team	0.0%	0
Community liaison officer	0.0%	0
Other (please specify)		0
answered question		**5**
skipped question		**12**

4. Did you consult any ethical guidelines in designing your trial? If so, which guidelines did you consult? (Tick as many as apply.)

		Response Percent	Response Count
National guidelines of host country		20.0%	1
National guidelines of sponsoring country		40.0%	2
National guidelines of researcher's institution		40.0%	2
CIOMS (Council for International Organisations of Medical Sciences)		20.0%	1
Declaration of Helsinki		**100.0%**	**5**
UNAIDS		20.0%	1
Nuffield Council on Bioethics		0.0%	0
NBAC (National Bioethics Advisory Commission)		0.0%	0
HPTN (HIV Prevention Trials Network)		0.0%	0
US Federal regulations (the Common rule)		40.0%	2
ICH-GCP (International Conference on Harmonization Good Clinical Practice		80.0%	4
Other (please specify)		20.0%	1
		answered question	**5**
		skipped question	**12**

5. At what stage(s) did you consult ethical guidelines?

	Response Percent	Response Count
I did not consult ethical guidelines	0.0%	0
Other members of the research team consulted ethical guidelines, but I did not	0.0%	0
In planning stages	60.0%	3
In planning stages and throughout the research process as required	**80.0%**	**4**
	Comment (optional)	0
	answered question	**5**
	skipped question	**12**

6. Was antiretroviral therapy provided to participants who seroconverted during the trial?

	Response Percent	Response Count
No	20.0%	1
Yes, through government programs	**40.0%**	**2**
Yes, through NGO programs	20.0%	1
Yes, through international donor programs	**40.0%**	**2**
Yes, directly linked to the research program	0.0%	0
Not sure	0.0%	0
	Please list any special provisions that assisted in antiretroviral access	1
	answered question	**5**
	skipped question	**12**

7. Are you aware of any ways in which your trial deviated from the research ethics guidelines you consulted?

		Response Percent	Response Count
No		20.0%	1
No, but compliance with the provision to ensure access to a proven product is uncertain		**40.0%**	**2**
Yes, some deviations were negotiated		**40.0%**	**2**
		Comment (optional)	1
		answered question	**5**
		skipped question	**12**

8. Where did you obtain ethics approval for your trial? Tick as many as apply.

		Response Percent	Response Count
In the host country		**100.0%**	**5**
In the sponsoring country		80.0%	4
In the country of the researcher's academic institution		40.0%	2
		Please name ethics committees used	3
		answered question	**5**
		skipped question	**12**

9. Did you negotiate the care that would be provided within the trial with communities affected by the trial?

		Response Percent	Response Count
No		**60.0%**	**3**
Yes, in planning stages		0.0%	0
Yes, in recruitment stages		0.0%	0
Yes, in planning and recruitment stages		0.0%	0
Yes, in planning and recruitment stages and through out the trial as required		40.0%	2
		Comment (optional)	1
		answered question	**5**
		skipped question	**12**

10. Was antiretroviral therapy provided to participants who seroconverted during the trial?

		Response Percent	Response Count
No		0.0%	0
Yes, through government programs		**40.0%**	**2**
Yes, through NGO programs		20.0%	1
Yes, through international donor programs		**40.0%**	**2**
Yes, directly linked to the research program		0.0%	0
Not sure		0.0%	0
	Please list any special provisions that assist in antiretroviral access		2
		answered question	**5**
		skipped question	**12**

11. Was antiretroviral therapy provided to volunteers found HIV positive at screening who were therefore ineligible to participate?

	Response Percent	Response Count
No	0.0%	0
Yes, through government programs	**40.0%**	**2**
Yes, through non-government programs	20.0%	1
Yes, through international donor programs	**40.0%**	**2**
Yes, directly linked to the research program	0.0%	0
Please list any special provisions that assist in antiretroviral access		1
answered question		**5**
skipped question		**12**

12. Did the trial offer medical/prevention services to participants?

		Response Percent	Response Count
No		0.0%	0
Yes, limited to conditions that would impact on the research findings (such as STIs)		40.0%	2
Yes, limited to conditions that would impact on the research (such as STIs) and conditions that are exacerbated by HIV (such as cervical dysplasia, TB)		0.0%	0
Yes, unlimited (except by site capacity)		**60.0%**	**3**
		Comment (please specify)	1
		answered question	**5**
		skipped question	**12**

13. Which benefits did the trial offer participants? Tick all that apply.

		Response Percent	Response Count
Counselling		**100.0%**	**5**
Male condoms		**100.0%**	**5**
Female condoms		20.0%	1
STI testing		80.0%	4
STI treatment		**100.0%**	**5**
Oral contraceptive pill		40.0%	2
Injectable contraception		40.0%	2
Contraceptive implants		20.0%	1
HPV vaccination		0.0%	0
Hepatitis B vaccination		20.0%	1
Male circumcision for partners/participants		40.0%	2
Cervical screening		20.0%	1
Treatment of cervical dysplasia		0.0%	0
		Comment (optional)	2
		answered question	**5**
		skipped question	**12**

14. Were health services offered to partners or families of participants?

		Response Percent	Response Count
No		**60.0%**	**3**
Yes		40.0%	2
		Comment (optional)	2
		answered question	**5**
		skipped question	**12**

15. Did your trial contribute infrastructure to the host country, e.g.the training of health care workers, establishment of clinical facilities?

		Response Percent	Response Count
No		0.0%	0
Yes (please specify)		**100.0%**	**5**
		answered question	**5**
		skipped question	**12**

16. Did the trial sponsor have policies regarding health/prevention services that were made available to participants?

		Response Percent	Response Count
No		**50.0%**	**2**
Yes		**50.0%**	**2**
		Comment (optional)	0
		answered question	**4**
		skipped question	**13**

17. How did sponsors' policies affect the care/prevention services offered to participants?

	Response Percent	Response Count
Sponsors did not have policies	25.0%	1
Sponsors' policies affected care/prevention services positively (increased or improved service range available)	**50.0%**	**2**
Sponsors' policies affected care/prevention services negatively (limited or decreased service range available)	25.0%	1
	Comment (optional)	1
	answered question	**4**
	skipped question	**13**

18. Were you satisfied that the trial adequately met its responsibilities to provide benefits and services to participants?

	Response Percent	Response Count
No	0.0%	0
Yes	**100.0%**	**5**
Partially	0.0%	0
Unsure	0.0%	0
	Comment (optional)	1
	answered question	**5**
	skipped question	**12**

19. Thank you for completing this questionnaire. Please tick the box below to exit

	Response Percent	Response Count
Exit now	**100.0%**	**5**
	answered question	**5**
	skipped question	**12**

20. This questionnaire will now ask a series of questions about the first trial you were involved in, then ask a series about the most recent trial you were involved in. What was the FIRST phase IIb or phase III HIV prevention intervention you were involved in testing?

	Response Percent	Response Count
PrEP	20.0%	2
Male circumcision	0.0%	0
HIV vaccine	10.0%	1
Microbicide	**30.0%**	**3**
PrEP/microbicide	0.0%	0
Treatment-as- prevention	0.0%	0
STI treatment for HIV prevention	20.0%	2
Diaphragm	20.0%	2
	Please list approximate start date of trial	9
	answered question	**10**
	skipped question	**7**

21. What was your role in the FIRST phase IIb or III HIV trial you were involved in?

		Response Percent	Response Count
Principal investigator		**55.6%**	**5**
Senior member of research team		44.4%	4
Community Liaison officer		0.0%	0
		Other (please specify)	3
		answered question	**9**
		skipped question	**8**

22. Did you consult any research ethics guidelines in the FIRST HIV prevention trial you were involved in? If so, whcih guidelines did you consult? Tick all that apply.

		Response Percent	Response Count
National guidelines of host country		54.5%	6
National guidelines of sponsoring country		54.5%	6
National guidelines of researcher's institution		54.5%	6
CIOMS (Council for International Organisations of Medical Sciences)		27.3%	3
Declaration of Helskini		**63.6%**	**7**
UNAIDS		36.4%	4
Nuffield Council on Bioethics		9.1%	1
NBAC (National Bioethics Advisory Commission)		0.0%	0
HPTN (HIV Prevention Trials Network)		27.3%	3
US Federal regulations (the Common Rule)		54.5%	6
ICH-GCP (International Conference on Harmonization Good Clinical Practice)		54.5%	6
		Other (please specify)	2
		answered question	**11**
		skipped question	**6**

23. Where did you obtain ethics approval for the FIRST HIV prevention trial in which you were involved? Tick all that apply.

	Response Percent	Response Count
In the host country	83.3%	10
In the sponsoring country	58.3%	7
In the country of the researcher's academic institution	**91.7%**	**11**
Please name ethics committees used		7
answered question		**12**
skipped question		**5**

24. Did you negotiate the care that would be provided within the trial with communities affected by the trial for the FIRST HIV prevention trial in which you were involved?

	Response Percent	Response Count
No	9.1%	1
Yes, in planning stages	**54.5%**	**6**
Yes, in recruitment stages	18.2%	2
Yes, in planning and recruitment stages	36.4%	4
Comment (optional)		3
answered question		**11**
skipped question		**6**

25. In the FIRST HIV prevention trial in which you were involved, was antiretroviral therapy provided to participants who seroconverted during the trial?

	Response Percent	Response Count
No	**50.0%**	**6**
Yes, through government programs	41.7%	5
Yes, through NGO programs	8.3%	1
Yes, through international donor programs	8.3%	1
Yes, directly linked to the research program	8.3%	1
Not sure	16.7%	2
Please list any special provisions that assisted in antiretroviral access		6
answered question		**12**
skipped question		**5**

26. In the FIRST HIV prevention trial in which you were involved, was antiretroviral therapy provided to volunteers found HIV positive at screening and therefore ineligible?

	Response Percent	Response Count
No	**66.7%**	**8**
Yes, through government programs	33.3%	4
Yes, through NGO programs	8.3%	1
Yes, through international donor programs	8.3%	1
Yes, directly linked to the research program	8.3%	1
answered question		**12**
skipped question		**5**

27. Did the FIRST HIV biomedical prevention trial you were involved in offer medical/prevention services to participants?

		Response Percent	Response Count
No		0.0%	0
Yes, limited to conditions that would impact on the research findings (such as STIs)		**54.5%**	**6**
Yes, limited to conditions that would impact on the research (such as STIs) and conditions that are exacerbated by HIV (such as cervical dysplasia, TB)		9.1%	1
Yes, unlimited (except by site capacity)		36.4%	4
		Comment (please specify)	1
		answered question	**11**
		skipped question	**6**

28. Which health/prevention services were offered to participants in the FIRST HIV prevention trial in which you were involved? Tick as many as apply.

	Response Percent	Response Count
Counselling	**100.0%**	**12**
Male condoms	**100.0%**	**12**
Female condoms	41.7%	5
STI testing	83.3%	10
STI treatment	**100.0%**	**12**
Oral contraceptive pill	50.0%	6
Injectable contraception	33.3%	4
Contraceptive implants	8.3%	1
HPV vaccination	8.3%	1
Hepatitis B vaccination	16.7%	2
Male circumcision for partners/participants	8.3%	1
Cervical screening	50.0%	6
Treatment of cervical dysplasia	0.0%	0
Referrals to local services for non-trial related illness/injury	83.3%	10
	answered question	**12**
	skipped question	**5**

29. In the FIRST HIV prevention trial you were involved in, were health services offered to partners or families of participants?

		Response Percent	Response Count
No		**58.3%**	**7**
Yes		41.7%	5
		Comment (optional)	2
		answered question	**12**
		skipped question	**5**

30. Did the FIRST HIV prevention trial you were involved with contribute infrastructure to the host country, e.g. training of health care workers, establishment of clinical facilities?

		Response Percent	Response Count
No		16.7%	2
Yes		**83.3%**	**10**
		Please specify	4
		answered question	**12**
		skipped question	**5**

31. In the FIRST prevention trial in which you were involved, did the trial sponsor have policies regarding health/prevention services that were made available to participants?

	Response Percent	Response Count
No	18.2%	2
Yes	**81.8%**	**9**
	Comment (optional)	2
	answered question	**11**
	skipped question	**6**

32. How did sponsors' policies affect the care/prevention services offered to participants in your FIRST biomedical prevention trial?

	Response Percent	Response Count
Sponsors did not have policies	10.0%	1
Sponsors' policies affected care/prevention services positively (increased or improved service range available)	**90.0%**	**9**
Sponsors' policies affected care/prevention services negatively (limited or decreased service range available)	0.0%	0
	Comment (optional)	2
	answered question	**10**
	skipped question	**7**

33. In the FIRST HIV prevention trial in which you were involved, were you satisfied that the trial adequately met its responsibilities to provide benefits and services to participants?

		Response Percent	Response Count
No		0.0%	0
Yes		**58.3%**	**7**
Partially		41.7%	5
Unsure		0.0%	0
		Comment (optional)	4
		answered question	**12**
		skipped question	**5**

34. This next section of the survey asks you about the MOST RECENT phase IIb or phase III biomedical HIV prevention intervention you have been involved in testing. What was the MOST RECENT phase IIb or phase III biomedical HIV prevention intervention you were involved in testing?

	Response Percent	Response Count
PrEP	**50.0%**	**6**
Male circumcision	16.7%	2
HIV vaccine	16.7%	2
Microbicide	8.3%	1
PrEP/microbicide	8.3%	1
Treatment-as- prevention	0.0%	0
STI treatment	0.0%	0
Diaphragm	0.0%	0
Please specify approximate start date of trial (year)		7
answered question		**12**
skipped question		**5**

35. What was your role in the MOST RECENT phase IIb or III biomedical HIV prevention trial you were involved in?

	Response Percent	Response Count
Principal investigator	**50.0%**	**5**
Senior member of research team	**50.0%**	**5**
Community Liaison officer	0.0%	0
Other (please specify)		3
answered question		**10**
skipped question		**7**

36. Did you consult any research ethics guidelines in the MOST RECENT HIV prevention trial you were involved in? If so, which guidelines did you consult? Tick all that apply.

	Response Percent	Response Count
National guidelines of host country	**81.8%**	**9**
National guidelines of sponsoring country	63.6%	7
National guidelines of researcher's institution	**81.8%**	**9**
CIOMS (Council for International Organisations of Medical Sciences)	27.3%	3
Declaration of Helsinki	72.7%	8
UNAIDS	63.6%	7
Nuffield Council on Bioethics	0.0%	0
NBAC (National Bioethics Advisory Commission)	0.0%	0
HPTN (HIV Prevention Trials Network)	45.5%	5
US Federal regulations (the Common Rule)	72.7%	8
ICH-GCP (international Conference on Harmonization Good Clinical Practice)	**81.8%**	**9**
Other (please specify)		1
answered question		**11**
skipped question		**6**

37. At what stage(s) in planning did you consult ethical guidelines? Tick as many as apply.

	Response Percent	Response Count
I did not consult guidelines	0.0%	0
Other members of the research team consulted guidelines, but I did not	0.0%	0
In planning stages	36.4%	4
In planning stages, and throughout the trial as required	**100.0%**	**11**
Comment (optional)		1
answered question		**11**
skipped question		**6**

38. Where did you obtain ethics approval for your MOST RECENT trial? Tick all that apply.

	Response Percent	Response Count
In the host country	**91.7%**	**11**
In the sponsoring country	66.7%	8
In the country of the researcher's academic institution	83.3%	10
Please name ethics committes used		7
answered question		**12**
skipped question		**5**

39. Did you consult with communities affected by the trial about the care/prevention services that would be provided within the trial in your MOST RECENT biomedical HIV prevention study?

	Response Percent	Response Count
No	0.0%	0
Yes, in planning stages	36.4%	4
Yes, in recruitment stages	27.3%	3
Yes, in planning and recruitment stages	81.8%	9
Yes, during the trial	**90.9%**	**10**
	Comment (optional)	0
	answered question	**11**
	skipped question	**6**

40. In the MOST RECENT biomedical HIV prevention trial in which you were involved, was antiretroviral therapy provided to participants who seroconverted during the trial?

	Response Percent	Response Count
No	0.0%	0
Yes, through government programs	**66.7%**	**8**
Yes, through NGO programs	33.3%	4
Yes, through international donor programs	25.0%	3
Yes, directly linked to the research program	33.3%	4
Not sure	0.0%	0
Please list any special provisions that assisted in antiretroviral access		3
answered question		**12**
skipped question		**5**

41. Which health/prevention services were offered to participants in the MOST RECENT biomedical HIV prevention trial in which you were involved? Tick as many as apply.

	Response Percent	Response Count
Counselling	**100.0%**	**12**
Male condoms	**100.0%**	**12**
Female condoms	66.7%	8
STI testing	91.7%	11
STI treatment	91.7%	11
Oral contraceptive pill	58.3%	7
Injectable contraception	58.3%	7
Contraceptive implants	8.3%	1
HPV vaccination	8.3%	1
Hepatitis B vaccination	41.7%	5
Male circumcision for partners/participants	33.3%	4
Cervical screening	58.3%	7
Treatment of cervical dysplasia	16.7%	2
Referrals to local services for non-trial related illness/injury	**100.0%**	**12**
	answered question	**12**
	skipped question	**5**

42. Did the MOST RECENT HIV biomedical prevention trial you were involved in offer medical/prevention services to participants?

	Response Percent	Response Count
No	0.0%	0
Yes, limited to conditions that would impact on the research findings (such as STIs)	**41.7%**	**5**
Yes, limited to conditions that would impact on the research (such as STIs) and conditions that are exacerbated by HIV (such as cervical dysplasia, TB)	16.7%	2
Yes, unlimited (except by site capacity)	**41.7%**	**5**
Comment (please specify)		2
answered question		**12**
skipped question		**5**

43. In the MOST RECENT HIV prevention trial you were involved in, were health/prevention services offered to partners or families of participants?

	Response Percent	Response Count
No	41.7%	5
Yes	**58.3%**	**7**
Comment (optional)		1
answered question		**12**
skipped question		**5**

44. Did the MOST RECENT HIV prevention trial you have been involved in contribute infrastructure to the host country, e.g.the training of health care workers, establishment of clinical facilities?

		Response Percent	Response Count
No		16.7%	2
Yes (please specify)		**83.3%**	**10**
		answered question	**12**
		skipped question	**5**

45. In the MOST RECENT prevention trial in which you were involved, did the trial sponsor have policies regarding health/prevention services that were made available to participants?

		Response Percent	Response Count
No		16.7%	2
Yes		**83.3%**	**10**
		Comment (optional)	1
		answered question	**12**
		skipped question	**5**

46. How did sponsors' policies affect the care/prevention services offered to participants in your MOST RECENT biomedical prevention trial?

	Response Percent	Response Count
Sponsors did not have policies	10.0%	1
Sponsors' policies affected care/prevention services positively (increased or improved service range available)	**90.0%**	**9**
Sponsors' policies affected care/prevention services negatively (limited or decreased service range available)	0.0%	0
Comment (optional)		2
answered question		**10**
skipped question		**7**

47. In the MOST RECENT HIV prevention trial in which you were involved, were you satisfied that the trial adequately met its responsibilities to provide benefits and services to participants?

	Response Percent	Response Count
No	0.0%	0
Yes	**100.0%**	**12**
Partially	0.0%	0
Unsure	0.0%	0
Comment (optional)		0
answered question		**12**
skipped question		**5**

Investigator/research staff questionnaire (final)

1. How many phase IIB or phase III biomedical HIV prevention trials have you been involved in? (Please include trials you are CURRENTLY involved in as well as those completed.)

	Response Percent	Response Count
One	29.4%	5
More than one	**70.6%**	**12**
	answered question	**17**
	skipped question	**0**

2. Which HIV prevention intervention have you been involved in testing?

	Response Percent	Response Count
PrEP	20.0%	1
HIV vaccine	0.0%	0
Male circumcision	**40.0%**	**2**
Microbicide	**40.0%**	**2**
PrEP/microbicide	0.0%	0
Treatment-as-prevention	0.0%	0
STI treatment as HIV prevention	0.0%	0
Diaphragm	0.0%	0
	Please specify approximate start date of trial	2
	answered question	**5**
	skipped question	**12**

3. What was your role in the trial or trials?

	Response Percent	Response Count
Principal investigator	**100.0%**	**5**
Senior member of research team	0.0%	0
Community liaison officer	0.0%	0
Other (please specify)		0
answered question		**5**
skipped question		**12**

4. Did you consult any ethical guidelines in designing your trial? If so, which guidelines did you consult? (Tick as many as apply.)

		Response Percent	Response Count
National guidelines of host country		20.0%	1
National guidelines of sponsoring country		40.0%	2
National guidelines of researcher's institution		40.0%	2
CIOMS (Council for International Organisations of Medical Sciences)		20.0%	1
Declaration of Helsinki		**100.0%**	**5**
UNAIDS		20.0%	1
Nuffield Council on Bioethics		0.0%	0
NBAC (National Bioethics Advisory Commission)		0.0%	0
HPTN (HIV Prevention Trials Network)		0.0%	0
US Federal regulations (the Common rule)		40.0%	2
ICH-GCP (International Conference on Harmonization Good Clinical Practice		80.0%	4
Other (please specify)		20.0%	1
		answered question	**5**
		skipped question	**12**

5. At what stage(s) did you consult ethical guidelines?

	Response Percent	Response Count
I did not consult ethical guidelines	0.0%	0
Other members of the research team consulted ethical guidelines, but I did not	0.0%	0
In planning stages	60.0%	3
In planning stages and throughout the research process as required	**80.0%**	**4**
	Comment (optional)	0
	answered question	**5**
	skipped question	**12**

6. Was antiretroviral therapy provided to participants who seroconverted during the trial?

	Response Percent	Response Count
No	20.0%	1
Yes, through government programs	**40.0%**	**2**
Yes, through NGO programs	20.0%	1
Yes, through international donor programs	**40.0%**	**2**
Yes, directly linked to the research program	0.0%	0
Not sure	0.0%	0
	Please list any special provisions that assisted in antiretroviral access	1
	answered question	**5**
	skipped question	**12**

7. Are you aware of any ways in which your trial deviated from the research ethics guidelines you consulted?

		Response Percent	Response Count
No		20.0%	1
No, but compliance with the provision to ensure access to a proven product is uncertain		**40.0%**	**2**
Yes, some deviations were negotiated		**40.0%**	**2**
		Comment (optional)	1
		answered question	**5**
		skipped question	**12**

8. Where did you obtain ethics approval for your trial? Tick as many as apply.

		Response Percent	Response Count
In the host country		**100.0%**	**5**
In the sponsoring country		80.0%	4
In the country of the researcher's academic institution		40.0%	2
		Please name ethics committees used	3
		answered question	**5**
		skipped question	**12**

9. Did you negotiate the care that would be provided within the trial with communities affected by the trial?

		Response Percent	Response Count
No		**60.0%**	**3**
Yes, in planning stages		0.0%	0
Yes, in recruitment stages		0.0%	0
Yes, in planning and recruitment stages		0.0%	0
Yes, in planning and recruitment stages and through out the trial as required		40.0%	2
		Comment (optional)	1
		answered question	**5**
		skipped question	**12**

10. Was antiretroviral therapy provided to participants who seroconverted during the trial?

		Response Percent	Response Count
No		0.0%	0
Yes, through government programs		**40.0%**	**2**
Yes, through NGO programs		20.0%	1
Yes, through international donor programs		**40.0%**	**2**
Yes, directly linked to the research program		0.0%	0
Not sure		0.0%	0
	Please list any special provisions that assist in antiretroviral access		2
		answered question	**5**
		skipped question	**12**

11. Was antiretroviral therapy provided to volunteers found HIV positive at screening who were therefore ineligible to participate?

	Response Percent	Response Count
No	0.0%	0
Yes, through government programs	**40.0%**	**2**
Yes, through non-government programs	20.0%	1
Yes, through international donor programs	**40.0%**	**2**
Yes, directly linked to the research program	0.0%	0
Please list any special provisions that assist in antiretroviral access		1
answered question		**5**
skipped question		**12**

12. Did the trial offer medical/prevention services to participants?

		Response Percent	Response Count
No		0.0%	0
Yes, limited to conditions that would impact on the research findings (such as STIs)		40.0%	2
Yes, limited to conditions that would impact on the research (such as STIs) and conditions that are exacerbated by HIV (such as cervical dysplasia, TB)		0.0%	0
Yes, unlimited (except by site capacity)		**60.0%**	**3**
		Comment (please specify)	1
		answered question	**5**
		skipped question	**12**

13. Which benefits did the trial offer participants? Tick all that apply.

		Response Percent	Response Count
Counselling		**100.0%**	**5**
Male condoms		**100.0%**	**5**
Female condoms		20.0%	1
STI testing		80.0%	4
STI treatment		**100.0%**	**5**
Oral contraceptive pill		40.0%	2
Injectable contraception		40.0%	2
Contraceptive implants		20.0%	1
HPV vaccination		0.0%	0
Hepatitis B vaccination		20.0%	1
Male circumcision for partners/participants		40.0%	2
Cervical screening		20.0%	1
Treatment of cervical dysplasia		0.0%	0
		Comment (optional)	2
		answered question	**5**
		skipped question	**12**

14. Were health services offered to partners or families of participants?

		Response Percent	Response Count
No		**60.0%**	**3**
Yes		40.0%	2
		Comment (optional)	2
		answered question	**5**
		skipped question	**12**

15. Did your trial contribute infrastructure to the host country, e.g.the training of health care workers, establishment of clinical facilities?

		Response Percent	Response Count
No		0.0%	0
Yes (please specify)		**100.0%**	**5**
		answered question	**5**
		skipped question	**12**

16. Did the trial sponsor have policies regarding health/prevention services that were made available to participants?

		Response Percent	Response Count
No		**50.0%**	**2**
Yes		**50.0%**	**2**
		Comment (optional)	0
		answered question	**4**
		skipped question	**13**

17. How did sponsors' policies affect the care/prevention services offered to participants?

	Response Percent	Response Count
Sponsors did not have policies	25.0%	1
Sponsors' policies affected care/prevention services positively (increased or improved service range available)	**50.0%**	**2**
Sponsors' policies affected care/prevention services negatively (limited or decreased service range available)	25.0%	1
	Comment (optional)	1
	answered question	**4**
	skipped question	**13**

18. Were you satisfied that the trial adequately met its responsibilities to provide benefits and services to participants?

	Response Percent	Response Count
No	0.0%	0
Yes	**100.0%**	**5**
Partially	0.0%	0
Unsure	0.0%	0
	Comment (optional)	1
	answered question	**5**
	skipped question	**12**

19. Thank you for completing this questionnaire. Please tick the box below to exit

	Response Percent	Response Count
Exit now	**100.0%**	**5**
	answered question	**5**
	skipped question	**12**

20. This questionnaire will now ask a series of questions about the first trial you were involved in, then ask a series about the most recent trial you were involved in. What was the FIRST phase IIb or phase III HIV prevention intervention you were involved in testing?

	Response Percent	Response Count
PrEP	20.0%	2
Male circumcision	0.0%	0
HIV vaccine	10.0%	1
Microbicide	**30.0%**	**3**
PrEP/microbicide	0.0%	0
Treatment-as- prevention	0.0%	0
STI treatment for HIV prevention	20.0%	2
Diaphragm	20.0%	2
	Please list approximate start date of trial	9
	answered question	**10**
	skipped question	**7**

21. What was your role in the FIRST phase IIb or III HIV trial you were involved in?

		Response Percent	Response Count
Principal investigator		**55.6%**	**5**
Senior member of research team		44.4%	4
Community Liaison officer		0.0%	0
		Other (please specify)	3
		answered question	**9**
		skipped question	**8**

22. Did you consult any research ethics guidelines in the FIRST HIV prevention trial you were involved in? If so, whcih guidelines did you consult? Tick all that apply.

		Response Percent	Response Count
National guidelines of host country		54.5%	6
National guidelines of sponsoring country		54.5%	6
National guidelines of researcher's institution		54.5%	6
CIOMS (Council for International Organisations of Medical Sciences)		27.3%	3
Declaration of Helskini		**63.6%**	**7**
UNAIDS		36.4%	4
Nuffield Council on Bioethics		9.1%	1
NBAC (National Bioethics Advisory Commission)		0.0%	0
HPTN (HIV Prevention Trials Network)		27.3%	3
US Federal regulations (the Common Rule)		54.5%	6
ICH-GCP (International Conference on Harmonization Good Clinical Practice)		54.5%	6
		Other (please specify)	2
		answered question	**11**
		skipped question	**6**

23. Where did you obtain ethics approval for the FIRST HIV prevention trial in which you were involved? Tick all that apply.

	Response Percent	Response Count
In the host country	83.3%	10
In the sponsoring country	58.3%	7
In the country of the researcher's academic institution	**91.7%**	**11**
Please name ethics committees used		7
answered question		**12**
skipped question		**5**

24. Did you negotiate the care that would be provided within the trial with communities affected by the trial for the FIRST HIV prevention trial in which you were involved?

	Response Percent	Response Count
No	9.1%	1
Yes, in planning stages	**54.5%**	**6**
Yes, in recruitment stages	18.2%	2
Yes, in planning and recruitment stages	36.4%	4
Comment (optional)		3
answered question		**11**
skipped question		**6**

25. In the FIRST HIV prevention trial in which you were involved, was antiretroviral therapy provided to participants who seroconverted during the trial?

	Response Percent	Response Count
No	**50.0%**	**6**
Yes, through government programs	41.7%	5
Yes, through NGO programs	8.3%	1
Yes, through international donor programs	8.3%	1
Yes, directly linked to the research program	8.3%	1
Not sure	16.7%	2
Please list any special provisions that assisted in antiretroviral access		6
answered question		**12**
skipped question		**5**

26. In the FIRST HIV prevention trial in which you were involved, was antiretroviral therapy provided to volunteers found HIV positive at screening and therefore ineligible?

	Response Percent	Response Count
No	**66.7%**	**8**
Yes, through government programs	33.3%	4
Yes, through NGO programs	8.3%	1
Yes, through international donor programs	8.3%	1
Yes, directly linked to the research program	8.3%	1
answered question		**12**
skipped question		**5**

27. Did the FIRST HIV biomedical prevention trial you were involved in offer medical/prevention services to participants?

		Response Percent	Response Count
No		0.0%	0
Yes, limited to conditions that would impact on the research findings (such as STIs)		**54.5%**	**6**
Yes, limited to conditions that would impact on the research (such as STIs) and conditions that are exacerbated by HIV (such as cervical dysplasia, TB)		9.1%	1
Yes, unlimited (except by site capacity)		36.4%	4
		Comment (please specify)	1
		answered question	**11**
		skipped question	**6**

28. Which health/prevention services were offered to participants in the FIRST HIV prevention trial in which you were involved? Tick as many as apply.

	Response Percent	Response Count
Counselling	**100.0%**	**12**
Male condoms	**100.0%**	**12**
Female condoms	41.7%	5
STI testing	83.3%	10
STI treatment	**100.0%**	**12**
Oral contraceptive pill	50.0%	6
Injectable contraception	33.3%	4
Contraceptive implants	8.3%	1
HPV vaccination	8.3%	1
Hepatitis B vaccination	16.7%	2
Male circumcision for partners/participants	8.3%	1
Cervical screening	50.0%	6
Treatment of cervical dysplasia	0.0%	0
Referrals to local services for non-trial related illness/injury	83.3%	10
	answered question	**12**
	skipped question	**5**

29. In the FIRST HIV prevention trial you were involved in, were health services offered to partners or families of participants?

		Response Percent	Response Count
No		**58.3%**	**7**
Yes		41.7%	5
		Comment (optional)	2
		answered question	**12**
		skipped question	**5**

30. Did the FIRST HIV prevention trial you were involved with contribute infrastructure to the host country, e.g. training of health care workers, establishment of clinical facilities?

		Response Percent	Response Count
No		16.7%	2
Yes		**83.3%**	**10**
		Please specify	4
		answered question	**12**
		skipped question	**5**

31. In the FIRST prevention trial in which you were involved, did the trial sponsor have policies regarding health/prevention services that were made available to participants?

	Response Percent	Response Count
No	18.2%	2
Yes	**81.8%**	**9**
	Comment (optional)	2
	answered question	**11**
	skipped question	**6**

32. How did sponsors' policies affect the care/prevention services offered to participants in your FIRST biomedical prevention trial?

	Response Percent	Response Count
Sponsors did not have policies	10.0%	1
Sponsors' policies affected care/prevention services positively (increased or improved service range available)	**90.0%**	**9**
Sponsors' policies affected care/prevention services negatively (limited or decreased service range available)	0.0%	0
	Comment (optional)	2
	answered question	**10**
	skipped question	**7**

33. In the FIRST HIV prevention trial in which you were involved, were you satisfied that the trial adequately met its responsibilities to provide benefits and services to participants?

		Response Percent	Response Count
No		0.0%	0
Yes		**58.3%**	**7**
Partially		41.7%	5
Unsure		0.0%	0
		Comment (optional)	4
		answered question	**12**
		skipped question	**5**

34. This next section of the survey asks you about the MOST RECENT phase IIb or phase III biomedical HIV prevention intervention you have been involved in testing. What was the MOST RECENT phase IIb or phase III biomedical HIV prevention intervention you were involved in testing?

	Response Percent	Response Count
PrEP	**50.0%**	**6**
Male circumcision	16.7%	2
HIV vaccine	16.7%	2
Microbicide	8.3%	1
PrEP/microbicide	8.3%	1
Treatment-as- prevention	0.0%	0
STI treatment	0.0%	0
Diaphragm	0.0%	0
Please specify approximate start date of trial (year)		7
answered question		**12**
skipped question		**5**

35. What was your role in the MOST RECENT phase IIb or III biomedical HIV prevention trial you were involved in?

	Response Percent	Response Count
Principal investigator	**50.0%**	**5**
Senior member of research team	**50.0%**	**5**
Community Liaison officer	0.0%	0
Other (please specify)		3
answered question		**10**
skipped question		**7**

36. Did you consult any research ethics guidelines in the MOST RECENT HIV prevention trial you were involved in? If so, which guidelines did you consult? Tick all that apply.

	Response Percent	Response Count
National guidelines of host country	**81.8%**	**9**
National guidelines of sponsoring country	63.6%	7
National guidelines of researcher's institution	**81.8%**	**9**
CIOMS (Council for International Organisations of Medical Sciences)	27.3%	3
Declaration of Helsinki	72.7%	8
UNAIDS	63.6%	7
Nuffield Council on Bioethics	0.0%	0
NBAC (National Bioethics Advisory Commission)	0.0%	0
HPTN (HIV Prevention Trials Network)	45.5%	5
US Federal regulations (the Common Rule)	72.7%	8
ICH-GCP (international Conference on Harmonization Good Clinical Practice)	**81.8%**	**9**
Other (please specify)		1
answered question		**11**
skipped question		**6**

37. At what stage(s) in planning did you consult ethical guidelines? Tick as many as apply.

	Response Percent	Response Count
I did not consult guidelines	0.0%	0
Other members of the research team consulted guidelines, but I did not	0.0%	0
In planning stages	36.4%	4
In planning stages, and throughout the trial as required	**100.0%**	**11**
Comment (optional)		1
answered question		**11**
skipped question		**6**

38. Where did you obtain ethics approval for your MOST RECENT trial? Tick all that apply.

	Response Percent	Response Count
In the host country	**91.7%**	**11**
In the sponsoring country	66.7%	8
In the country of the researcher's academic institution	83.3%	10
Please name ethics committes used		7
answered question		**12**
skipped question		**5**

39. Did you consult with communities affected by the trial about the care/prevention services that would be provided within the trial in your MOST RECENT biomedical HIV prevention study?

	Response Percent	Response Count
No	0.0%	0
Yes, in planning stages	36.4%	4
Yes, in recruitment stages	27.3%	3
Yes, in planning and recruitment stages	81.8%	9
Yes, during the trial	**90.9%**	**10**
	Comment (optional)	0
	answered question	**11**
	skipped question	**6**

40. In the MOST RECENT biomedical HIV prevention trial in which you were involved, was antiretroviral therapy provided to participants who seroconverted during the trial?

	Response Percent	Response Count
No	0.0%	0
Yes, through government programs	**66.7%**	**8**
Yes, through NGO programs	33.3%	4
Yes, through international donor programs	25.0%	3
Yes, directly linked to the research program	33.3%	4
Not sure	0.0%	0
Please list any special provisions that assisted in antiretroviral access		3
answered question		**12**
skipped question		**5**

41. Which health/prevention services were offered to participants in the MOST RECENT biomedical HIV prevention trial in which you were involved? Tick as many as apply.

	Response Percent	Response Count
Counselling	**100.0%**	**12**
Male condoms	**100.0%**	**12**
Female condoms	66.7%	8
STI testing	91.7%	11
STI treatment	91.7%	11
Oral contraceptive pill	58.3%	7
Injectable contraception	58.3%	7
Contraceptive implants	8.3%	1
HPV vaccination	8.3%	1
Hepatitis B vaccination	41.7%	5
Male circumcision for partners/participants	33.3%	4
Cervical screening	58.3%	7
Treatment of cervical dysplasia	16.7%	2
Referrals to local services for non-trial related illness/injury	**100.0%**	**12**
	answered question	**12**
	skipped question	**5**

42. Did the MOST RECENT HIV biomedical prevention trial you were involved in offer medical/prevention services to participants?

	Response Percent	Response Count
No	0.0%	0
Yes, limited to conditions that would impact on the research findings (such as STIs)	**41.7%**	**5**
Yes, limited to conditions that would impact on the research (such as STIs) and conditions that are exacerbated by HIV (such as cervical dysplasia, TB)	16.7%	2
Yes, unlimited (except by site capacity)	**41.7%**	**5**
Comment (please specify)		2
answered question		**12**
skipped question		**5**

43. In the MOST RECENT HIV prevention trial you were involved in, were health/prevention services offered to partners or families of participants?

	Response Percent	Response Count
No	41.7%	5
Yes	**58.3%**	**7**
Comment (optional)		1
answered question		**12**
skipped question		**5**

44. Did the MOST RECENT HIV prevention trial you have been involved in contribute infrastructure to the host country, e.g.the training of health care workers, establishment of clinical facilities?

		Response Percent	Response Count
No		16.7%	2
Yes (please specify)		**83.3%**	**10**
		answered question	**12**
		skipped question	**5**

45. In the MOST RECENT prevention trial in which you were involved, did the trial sponsor have policies regarding health/prevention services that were made available to participants?

		Response Percent	Response Count
No		16.7%	2
Yes		**83.3%**	**10**
		Comment (optional)	1
		answered question	**12**
		skipped question	**5**

46. How did sponsors' policies affect the care/prevention services offered to participants in your MOST RECENT biomedical prevention trial?

	Response Percent	Response Count
Sponsors did not have policies	10.0%	1
Sponsors' policies affected care/prevention services positively (increased or improved service range available)	**90.0%**	**9**
Sponsors' policies affected care/prevention services negatively (limited or decreased service range available)	0.0%	0
Comment (optional)		2
answered question		**10**
skipped question		**7**

47. In the MOST RECENT HIV prevention trial in which you were involved, were you satisfied that the trial adequately met its responsibilities to provide benefits and services to participants?

	Response Percent	Response Count
No	0.0%	0
Yes	**100.0%**	**12**
Partially	0.0%	0
Unsure	0.0%	0
Comment (optional)		0
answered question		**12**
skipped question		**5**