Socio-behaviour challenges to phase III HIV vaccine trials in Sub-Saharan Africa

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Abstract

Background: A number of countries in sub-Saharan Africa are preparing for HIV vaccine efficacy trials. Social and behavioural factors related to HIV transmission require examination in each setting where these trials are considered. As part of this, several countries have also recently begun preparatory research investigating relevant social and behavioural issues. There is a need for a review of the literature to help focus such research efforts in Sub-Saharan Africa.

Objective: To examine key social and behavioural issues that may impact on the conduct of HIV vaccine efficacy trials in sub-Saharan Africa.

Design: Literature review

Methods: Major databases (PubMed, PsychInfo, EBSCOhost, and AIDSline) were searched for literature that discussed social and behavioural issues related to HIV vaccine trials. Three areas are highlighted as being particularly significant for HIV vaccine research: (1) willingness to participate in future HIV vaccine efficacy trials, (2) retention of participants in studies, and (3) sexual risk reporting during trials. For each of these topics, major findings from both developed and developing countries are described and avenues for further research are discussed.

Results: There are few data from Sub-Saharan Africa regarding willingness to participate in HIV vaccine trials. Data on participant retention rates varies widely, and maintaining large cohorts of individuals within Phase III trials presents an important challenge. In addition, the possible impact of trial participation on sexual disinhibition, and response bias on sexual risk-reporting remain as issues for HIV vaccine trials in African contexts.

Conclusions: Social and behavioural research forms an important part of preparations for HIV vaccine efficacy trials, and there is a clear need for more research of this type in Sub-Saharan Africa. Innovative approaches are required to address issues such as willingness to participate in vaccine research, participant retention during efficacy trials, and the accurate reporting by participants of sexual risk behaviours.

Key words: Africa, HIV, vaccines, clinical trials, preparation, behaviour, review

African Health Sciences 2005;5(3):198-206

Introduction

More than twenty years after the start of the epidemic, HIV/AIDS remains one of the most important threats to health around the globe.[1] Sub-Saharan Africa is heavily affected by the epidemic with 25 million people currently infected and an estimated 3 million new infections every year.[2] A range of structural and personal level factors have been thought to contribute to the rapid spread of the epidemic in Africa. Major structural factors include social, economic and healthcare development[3] including reduction of poverty and gender-based violence.[4;5] Individual-level factors include sexual risk behaviours such as transactional sex, age of sexual debut, number of sexual partners, and low condom use.[5-7] Despite moderate successes in decreasing individual-level risk[8], and international efforts to address structural factors[9;10], the epidemic continues unabated. In this light, an affordable and effective HIV vaccine remains vitally important to curtailing the population-level spread of infection.

Clinical trials for HIV vaccines include three distinct phases: Phase I trials are conducted on a small number

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of healthy humans at low risk for HIV infection to assess safety. Phase II trials use larger numbers (several hundreds) of low risk individuals to build on this safety data and also assess immunogenicity. A range of scientific[14;15] and ethical issues[16] needs to be considered before moving to phase III trials, which is one of the reasons why few such trials have taken place since the start of HIV vaccine development.[1] Phase III HIV vaccine trials are conducted on large numbers of people (several thousands) at high risk for HIV infection which is currently defined as an HIV incidence rate of 2% or more.[17] These trials usually take a number of years to complete and require participants to return for frequent HIV tests and immunizations.[17]

Despite acknowledging the need for an HIV vaccine, progress has been slow for many resource-poor countries.[1;11] Of the phase I and II HIV vaccine trials that have taken place globally, most have been conducted in the United States (US) and Europe with only four phase I and II trials completed, or currently in progress in sub-Saharan Africa (see also www.iavi.org for list of preventative trials to date).[1] The first phase III HIV vaccine trials have recently been completed in North America and Thailand (AIDSVAX B/B and AIDSVAX B/E, respectively; VaxGen Inc, Brisbane, CA, USA).[12] Thailand has also been the only developing country that has been part of a phase III trial, and has also had more phase I and II trials than any other developing country.[13]

Phase III HIV vaccine trials to date have largely focused on sub-groups most at risk for HIV infection, such as commercial sex workers (CSW), intravenous drug-users (IDU), and men who have sex with men (MSM). The AIDSVAX B/B trial (North America) recruited mainly MSM and the AIDSVAX B/E study (Thailand) focused on prevention against blood-borne infection in IDU.[12] These trials therefore targeted specific populations known to be at high risk for HIV infection. In contrast, the epidemic in sub-Saharan Africa is most severe in heterosexual men and women[2;18] who may not consider themselves to be at high risk for HIV infection and perceive obvious benefits to volunteering for phase III trials. Sub-Saharan Africa is also characterised by great social, economic and political diversity, with high rates of migration[19], political unrest[20], a lack of sustained, stable infrastructure[20;21], and low literacy levels[22]. In many respects these factors present a challenge to the conduct of phase III vaccine trials.

Moreover before the first phase III trials commenced a range of issues were discussed in the literature pertaining to both developed[17;23;24] and less-developed countries. [25-28] While the AIDSVAX trials refuted many of these concerns[29;30] they remain important in countries where trials have not taken place. Key issues addressed by these studies include:

a) whether it will be possible to recruit and retain the large numbers of at-risk individuals over long time-periods as required for phase III trials[31-34]
b) whether high-risk individuals from the general population be willing to enroll in these trials, [32;33] and
c) whether trial participation will result in an increase, rather than decrease in sexual behaviour due to a false sense of protection by the vaccine.[35;36]

Researchers working in HIV vaccine trials describe these and related issues using the collective term *social and behavioural issues*. Given the importance of an effective HIV vaccine for addressing the HIV/AIDS epidemic in sub-Saharan Africa, and the growing movement to test experimental HIV vaccines in different parts of the continent, here we review existing evidence regarding the social and behavioural issues involved in HIV vaccine trials. We use this review to help highlight topics that require attention as part of future research to prepare for upcoming HIV vaccine trials.

Methods

The aims of this review were to (a) report on the key findings of social and behavioural research conducted to date involving HIV vaccine trials; (b) to use these findings to identify the important topics emerging from this literature; (c) to compare major findings from Africa with the rest of the world, and (d) to suggest areas for further research in Africa as part of preparations for Phase III efficacy trials.

Search strategy

Data for this review were identified by: searches of the electronic databases Medline (PubMed), PsychInfo, EBSCOhost and AIDSline. These databases were chosen because they provide comprehensive coverage of peer-reviewed social and behavioural research involving HIV/AIDS. Search terms used in electronic databases were "HIV/AIDS", " vaccine", "vaccine trials", "risk behaviours", "reporting" and "trial participation", with different combinations of these search terms used to identify articles that met the selection requirements. We also identified materials through references from relevant articles and contacting investigators working in this field

throughout sub-Saharan Africa. Numerous articles were identified through searches of the extensive files of the authors. English and French language papers were eligible for the review.

Research findings from HIV vaccine preparedness and clinical trials were then collated for both developed (United States and Europe) and developing countries. One-thousand and fifty-nine articles were found that discussed HIV vaccines and clinical trials; of these 204 articles discussed issues related to behaviour and 208 articles discussed clinical trials in Africa. Only 86 articles discussed HIV clinical trials in African countries.

Inclusion Criteria

As part of an ongoing programme of social and behavioural research under the auspices of the South African AIDS Vaccine Initiative (SAAVI) we identified three key topics that are particularly important for work in sub-Saharan Africa to form the basis for this review:

a) Willingness to participate in future phase III HIV vaccine trials;
b) Retention during trials; and,
c) Sexual risk behaviour and reporting of risk behaviour during trials.

Exclusion criteria

The following areas, although considered significant, were excluded or limited in the review of literature and subsequent discussion:

a) Ethical issues during HIV vaccine trials are discussed only as they pertain to the issues above. The impact of discrimination during trials may be a major concern in African countries where HIV-related stigma have been documented.[37-42] A number of studies have examined the impact of trial-related discrimination,[23;43;44] and the reader is referred to these texts for a full discussion.
b) Economic (site selection, financial impact, etc), statistical (sample size, trial endpoints) and scientific concerns (level and type of induced immunity, host genetics) were excluded from the review. However the literature in these areas is comprehensive and the interested reader are referred to these reviews.[45-47]
c) Since HIV transmission in sub-Saharan Africa occurs predominantly in heterosexual populations this review will focus only on sexual behaviours pertaining to this population,[48-50] and exclude other forms of transmissions such as needle-sharing during intravenous drug-use or sexual practices related to MSM, for example.

Results and Discussion

Willingness to participate in future phase III HIV vaccine trials

For phase III HIV vaccine trials to be feasible, high risk groups must endorse and be willing to participate in such trials.[51;52] However, reported Willingness To Participate (WTP) in phase III HIV vaccine trials have varied greatly between studies. In America, WTP in future efficacy trials ranged from 91% in MSM[53] to 27% in a mixed group of MSM, IDU and high-risk women.[54] Among army conscripts, 25 to 30% were willing to participate in Thailaind,[55-57] while 80% endorsed such trials in Uganda.[58]

Reported WTP in hypothetical trials does not necessarily guarantee enrolment into an actual trial. An American study reported that only 29% of those who indicated "definitely willing" and 16% of those who indicated "probably willing" to take part in a HIV vaccine trial during the preparedness study actually enrolled.[59] Similarly, less than 50% of those enrolled in a preparedness cohort, who stated that they would take part in a phase III vaccine trial, eventually enrolled into the North American AIDSVAX trial.[52]

Reasons for non-participation in trials include fears that the vaccine may not be safe for humans;[53;54;56;60] may cause side-effects[44;56-58] or AIDS,[54;55] or that they may be discriminated against.[53-56;60] Reported WTP may also be influenced by negative media reports,[61] and by increased knowledge of vaccine trials with data suggesting that the more participants knew about HIV vaccines and clinical trials, the less likely they were to participate.[59;62-64]

Despite this, many participants remained willing to participate in vaccine trials. Selfless aims such as altruism[56;65;66] and a desire to fight AIDS[53;58;67] have often been cited as motivating factors. Material benefits such as free medical care[58] and monetary compensation have also been reported as important factors, especially in resource-poor settings.[56;57]

Studies also examined the differences between participants who remained positive about participation and those who eventually changed their minds after receiving information about the risks involved. These studies found that those who remained willing reported more risk behaviour[52;54;62;68;69] and were often younger and more depressed compared to those who declined participation.[52] More importantly, WTP has also been associated with low socio-economic status and education,[52;54;62] and with a greater difficulty in understanding vaccine-related con-

cepts.[68] This raises important ethical questions about the inclusion of vulnerable populations in clinical trials.[25;70]

Measuring willingness to participate

The decision to take part in a HIV vaccine efficacy trial is embedded within a context of personal, emotional and cognitive factors. Cross-sectional studies often strip the answer (willing or not) from these contexts and does not provide insight into how different contexts may influence decision-making.[57;58;71] Another limitation is that it may be less important to know whether someone is willing or not willing at a particular point in time, but what factors influence this decision-making process. For example, it has been suggested that African people may have entirely different ways of making decisions about trial participation since their concept of self is defined in affiliation with the larger group, compared to Westerners whose decision-making may primarily be based on individual terms.[27] While this has been widely contested by others,[72] it has encouraged informed consent procedures to take cultural differences into account.[73;74] Yet, whether and what cultural factors impact on decision-making related to phase III trial participation remains uncertain and requires investigation.

Areas for further research

1. Data on the willingness to participate in future HIV vaccine efficacy trials are required for different African countries..
2. Reported willingness must be compared with actual enrolment into phase I/II trials in the same study population. This will be important to ascertain whether stated willingness corresponds to actual enrolment before commencing to phase III trials.
3. The relationship between knowledge of HIV vaccine trials and WTP has not been examined in countries with low literacy levels.
4. More research needs to focus on the impact of culture and social context on decision-making as well as how individual factors (age, gender, knowing someone with HIV, emotional states) interact with culture and social factors during decision-making.
5. Innovative ways to examine and address issues about participation are required to ensure that participants make informed decisions.

Retention and attrition

The ability to recruit and retain large numbers of participants is a key concern in HIV vaccine efficacy trials.[24] Before the first phase III trials were conducted, longitudinal studies examined recruitment and retention in a range of different sub-groups in America.[34] These studies reported the ability to retain between 70 - 90% of participants between 9 and 18 months after enrollment,[31;75] which suggested that phase III trials would indeed be feasible. Similarly, studies in Thailand reported high retention rates - about 90% in CSW, army conscripts and MSM.[76] The retention rates of the two AIDSVAX trials have not yet been made available, but early reports suggest that retaining participants, while possible, were not without difficulties and required an extensive investment from study staff.[12]

Retention data from other forms of HIV prevention research are highly variable. In studies of HIV prevention in pregnancy in Uganda, for example, very low rates of attrition have been maintained over relatively long periods [77], while researchers working with CSW in Kenya reported high drop-out rates (up to 33.7% after enrolment) and a very high attrition rate due to seroconversion (37% in the first year).[78]

Reasons for retention and/or attrition

Incarceration, migration and homelessness constituted major problems in finding participants who missed their follow-up visits in longitudinal studies of inner city drug-users in the USA.[79;80] The North American AIDSVAX trial, which also recruited IDU reported similar reasons for attrition.[12] In contrast, in African studies, attrition was associated with higher risk behaviour and fear of knowing your HIV status in heterosexual population in Kenya and Tanzania.[78;81] This suggests that factors related to attrition may differ between population groups, and may require different approaches to retention.

Retention strategies

Sixty recruitment sites were strategically located across a large geographic region during the North American AIDSVAX trial. This prevented loss-to-follow-up due to migration since participants could be transferred to another recruitment site in a neighbouring area.[12] Other studies have formed alliances with social service agencies (governmental and other) to track participants[12;79] or provided counselling, assistance with housing and employment, food parcels, toiletries and small gifts.[79;82] However, a concern is that providing incentives for retention in populations where even basic provisions are limited may have ethical implications.[25] Logistical factors, such as travelling long distances to trial-sites, inadequate roads, a lack of public transport and electricity may also

negatively impact retention in these settings. Retention strategies require a significant investment in human, financial and technological resources, which can be costly and time-consuming. It is therefore imperative to understand attrition in different context, to be able to intervene effectively and in a resource-efficient manner during efficacy trials.

Areas for further research

1. Diverse retention rates have been noted across studies. Research needs to examine what factors impact on retention.
2. While innovative recruitment and retention strategies are needed, the ethical implications of these on vulnerable populations need to be assessed.
3. It is uncertain what infrastructure, resources and technology are required to optimize retention in African contexts.
4. Creative retention strategies need to be piloted in different settings to determine cost-effective ways of retaining participants.

Sexual risk monitoring

Apart from the challenge of retaining trial participants, there is also a concern that participants in a vaccine trial may increase their risk-taking behaviour by thinking the vaccine is protective against infection. A range of studies, including phase I and II trials, have reported that participants either increased or stated that they would increase their risk behaviour if part of a vaccine trial.[35;36;65;68;77;83;84] Concerns have been raised that this may lead to a perverse outcome where phase III HIV vaccine trials result in more, rather than less HIV infections.[36] Related to this, condom distribution and promotion for sexual risk reduction is a necessary component of HIV vaccine trials, though there is no evidence to suggest that increasing the availability or accessibility of condoms alters sexual activity itself.[85]

For ethical reasons it is thus essential that HIV risk behaviours are carefully monitored and that effective risk reduction procedures are in place to prevent sexual disinhibition during trials. Apart from the fact that there is little data available on sexual disinhibition during trials, another concern is that the reliability of sexual risk-reporting is constrained by memory biases and a range of demand characteristics[86], which have been shown to negatively impact on vaccine preparedness research in developed countries[87] and must also be addressed in African contexts.

Measuring sexual risk behaviour

Since ethical and practical issues prevent measuring sexual behaviour through direct observation, research on sexual behaviour aims to provide conditions that will facilitate reliable and valid reports. The assumption is that honest reports are more accurate and will increase when privacy and anonymity is assured.[88;89] Self-administered questionnaires are thus preferred as they offer more privacy than face-to-face interviews, but requires a high level of literacy and familiarity with questionnaire completion.[88] In cases where this is not possible interviews remain the best method to obtain information of sensitive behaviours. However, this method can introduce response biases which may affect the accuracy of the data.[90;91]

Social desirability is one of the key biases that can influence data based on self-report. It refers to self-presentation, a tendency to present personal information in a way that will enhance one's status in interpersonal situations.[90] In HIV research where safe sexual practices may be considered desirable, participants may thus bias their responses accordingly, especially when negative outcomes are feared.[86;90;92] Social desirability may also be prominent when there is a large discrepancy in race, class or social status between the researcher and respondent, which is often the case when research is conducted in African contexts.[25;93]

Recently computer-assisted self-interviewing (CASI) has been examined as an alternative method of assessment to overcome the limitations inherent in the interviewing process. This involves the use of a computer where questions are either visibly displayed or asked by the computer in an audio-format (called audio-CASI or ACASI).[94] This is useful in low-literacy populations were respondents can listen to the questions on earphones and reply by pressing clearly marked keys on the keyboard or a touch-screen.[94;95] This technology has many advantages compared to paper-and-pencil tests such as increased privacy, fewer problems related to multi-lingual and low literacy contexts, and also ensures a fully standardized data-collection procedure.[94-96] CASI or ACASI has been successfully used in general population surveys,[97] as well as with high-risk groups such as adolescents,[94;98] and IDU.[99] However, there is still debate whether CASI is more reliable than pen-and-paper tests or interviews,[100] and the acceptability of this technology has not been established in sub-Saharan Africa. A study in Zimbabwe suggested that unfamiliarity with technology may be a barrier against effective usage in rural, low literacy populations.[96]

Cultural and religious beliefs against talking about sex may however be less responsive to methodological advancements.[90;101] In societies where strong cultural or religious taboos exist, research on sexual behaviour may

not only be inaccurate, but also considered offensive.[102;103] In addition, urbanization may mediate cultural taboos, resulting in differential levels of sexual self-disclosure between members of the same cultural group,[90] and more variability in the accuracy of sexual risk reporting in these regions.[104] Ways to improve the acceptability of sexual research in these settings are complex but essential for phase III HIV vaccine trial preparations.

Areas for further research

1. Longitudinal studies need to examine changes in self-reported sexual risk behaviour over time to examine sexual disinhibition and the effectiveness of risk reduction counseling.
2. Culturally-attuned ways to examine sexual risk reporting related to HIV infection are required.
3. More research on CASI, ACASI and other methods are needed in sub-Saharan Africa to establish their appropriateness for use in low literacy populations who may be unfamiliar with technology.
4. Research needs to establish whether and how cultural and religious factors impact on sexual risk disclosure.

Conclusion

Socio-behavioural research is essential in preparing for HIV vaccine efficacy trials and should be strengthened in sub-Saharan Africa. Few data exist on how different cultural, economic and social contexts may influence the decision to enter a trial, the reasons for leaving a trial and the honest reporting of sexual risk behaviour and needs further investigation.

Acknowledgements

The authors wish to thank Catherine Slack and Cecilia Milford from the HIV/AIDS Vaccines Ethics Group (HAVEG) University of Kwa-Zulu Natal for providing valuable comments on various drafts of this paper. This work was supported by the South African AIDS Vaccine Initiative (SAAVI).

References

1. Esparza J, Bhamarapravati N. Accelerating the development and future availability of HIV-1 vaccines: why, when, where, and how? Lancet 2000; 355: 2061-6.
2. UNAIDS. *Fourth global report on the AIDS epidemic*. Geneva, Switzerland: UNAIDS, 2004.
3. Parker R. The global HIV/AIDS pandemic, structural inequalities and the politics of international health. *Am J Public Health* 2002; 92: 343-6.
4. Myer L, Morroni C, Susser ES. The social pathology of the HIV/AIDS pandemic. *Int J Epidemiol* 2003; 32: 189-192.
5. Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntyre JA, Harlow SD. Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa. Lancet 2004; 363: 1415-21.
6. MacPhail C, Campbell C. 'I think condoms are good but, aai, I hate those things': condom use among adolescents and young people in a Southern African township. Soc Sci Med 2001; 52: 1613-27.
7. Little F, Myer L, Mathews C. Barriers to accessing free condoms at public health facilities across South Africa. *S Afr Med J* 2002; 92: 218-20.
8. Stoneburner RL, Low-Beer D. Sexual partner reductions explain human immunodeficiency virus declines in Uganda: comparative analyses of HIV and behavioural data in Uganda, Kenya, Malawi, and Zambia. *Int J Epidemiol* 2004; 33: 624.
9. Cohen DA, Scribner R. An STD/HIV prevention intervention framework. AIDS Patient Care STD 2000; 14: 37-45.
10. Gupta GR. Gender and HIV / AIDS: transforming prevention programs. AidsCaptions. 1995; 2: 8-10.
11. Tucker TJ, Mazithulela G. Development of an AIDS vaccine: perspective from the South African AIDS Vaccine Initiative. BMJ 2004; 329: 454-6.
12. Francis DP, Heyward WL, Popovic V, Orozco-Cronin P, Oreland K, Gee C. Candidate HIV/AIDS vaccines: lessons learned from the world's first phase III efficacy trials. AIDS 2003; 17: 147-56.
13. Weidle PJ, Mastro T D, Grant AD, Nkengasong J, Macharia D. HIV/AIDS treatment and HIV vaccines for Africa. Lancet 2002; 359: 2261-2267.
14. Burton DR, Desrosiers RC, Doms RW, Feinberg MB, Gallo RC, Hahn B. A Sound Rationale Needed for Phase III HIV-1 Vaccine Trials. Science 2004; 303: 316.
15. Vermund SH. Vaccine Efficacy Trials for Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Are Feasible in the United States: A Commentary on the HIVNET Vaccine Preparedness Study. *Am J Epidemiol* 2001; 153: 628-31.
16. Cohen J. No Consensus on Rules for AIDS Vaccine Trials. Science 1998; 281: 22-3.
17. Temoshok LR. Behavioral research contributions to planning and conducting HIV vaccine efficacy studies. AIDS Res Hum Retroviruses 1994; 10: s277-s280.
18. World Health Organisation. Future access to HIV vaccines. Report from a WHO-UNAIDS Consultation, Geneva, 2-3 October 2000. *AIDS* 2001; 15: w27-w44.
19. Lurie, M. Migration and AIDS in southern Africa: A review. *S A J Sci* 2000; 96: 343-346.
20. Awotona A. Approaches to post-war reconstruction and development : Lessons from Africa. Habitat International 1992; 16: 79-98.
21. Alubo SO. Debt crisis, health and health services in Africa. Soc Sci Med 1990; 31: 639-48.
22. Benedicta E. Femanomics, women literacy and economics in

Sub Saharan Africa. Equal Opportunities International 2000; 19: 8-16.
23. Chesney MA, Lurie P, Coates TJ. Strategies for addressing the social and behavioral challenges of prophylactic HIV vaccine trials. *J Acquir Imune Defic Syndr Hum Retrovirol* 1995; 9: 30-5.
24. Grinstead OA. Social and behavioral issues in phase III HIV preventive vaccine trials. AIDS 1995; 9: s245-s250.
25. Lindegger G, Slack C, Vardas E. HIV vaccine trials in South Africa—some ethical considerations. *S Afr Med J* 2000; 90: 769-72.
26. Lurie P, Bishaw M, Chesney MA, Cooke M, Fernandes ME, Hearst N. Ethical, behavioral, and social aspects of HIV vaccine trials in developing countries. *JAMA* 1994; 271: 295-301.
27. Moodley K. HIV Vaccine Trial participation in South Africa: An ethical assessment. *J Med Philos* 2002; 27: 197-215.
28. Mugenyi PN. HIV vaccines: the Uganda experience. Vaccine 2002; 20: 1905-8.
29. Bass E. VaxGen trial yields trove of behavioural and social science findings. IAVI Report 2003; 7: 1.
30. Van Griensvan F, Keawkungwal J, Tappero JW, Sangkum U, Pitisuttithum P, Vanichseni S. Lack of increased HIV risk behavior among injection drug users participating in the AIDSVAX B/E HIV vaccine trial in Bangkok, Thailand. AIDS 2004; 18: 295-301.
31. Koblin BA, Taylor PE, Avrett S, Stevens CE. The feasibility of HIV-1 vaccine efficacy trials among gay/bisexual men in New York City: Project ACHIEVE. AIDS Community Health Initiative Enroute to the Vaccine Effort. AIDS 1996; 10: 1555-61.
32. Sheon AR. Overview: HIV vaccine feasibility studies. AIDS Res Hum Retroviruses 1994; 10: s195-s196.
33. Vermund SH. The role of prevention research in HIV vaccine trials. AIDS Res Hum Retroviruses 1994; 10: s303-s305.
34. Seage GR, Holte S, Metzger D, Koblin BA, Gross M, Celum C. Are US populations appropriate for trials of human immunodeficiency virus vaccine? *Am J Epidemiol* 2001; 153: 619-627.
35. Blower SM, McLean AR. Prophylactic vaccines, risk behaviour change, and the probability of eradicating HIV in San Francisco. Science 1994; 265: 1451-1454.
36. Chesney MA, Chambers DB, Kahn JO. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: a cautionary note. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; 16: 266-71.
37. Piot, P. *Report by the executive director. Joint United Nations Programme on AIDS*. Presented in Rio de Janeiro, 15-16 December. 2002.
38. UNAIDS. *An overview of HIV/AIDS related stigma*. Geneva: UNAIDS, 2004.
39. UNAIDS. *HIV/AIDS related stigma and discrimination. A review and suggested ways forward for South Asia.* Geneva: UNAIDS, 2002.
40. Baleta A. South African faces an AIDS crisis as government health campaigns fail. Lancet 1999; 353: 653.
41. Maduna-Butshe AC. Women sex workers and the HIV pandemic: stigma and blame in context. SAfAIDS News 1997; 5: 8-11.
42. Muyinda H, Seeley J, Pickering H, Barton T. Social aspects of AIDS-related stigma in rural Uganda. Health Place 1997; 3: 143-7.
43. Allen M, Israel H, Rybczyk K, Pugliese MA, Loughran K, Wagner L. Trial-related discrimination in HIV vaccine clinical trials. AIDS Res Hum Retroviruses 2001; 17: 667-74.
44. Thapinta D, Jenkins RA, Celentano DD, Nitayaphan S, Buapunth P, Triampon A. Evaluation of behavioral and social issues among Thai HIV vaccine trial volunteers. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; 20: 308-14.
45. Esparza J, Osmanov S. HIV vaccines: A global perspective. Curr Mol Med 2003; 3: 183-93.
46. Garber DA, Silvestri G, Feinberg MB. Prospects for an AIDS vaccine: three big questions, no easy answers. Lancet Infect Dis 2004; 4: 397-413.
47. Hoth DF, Bolognesi DP, Corey L, Vermund SH. HIV Vaccine Development: A Progress Report. Ann Intern Med 1994; 121: 603-11.
48. Johnson AM, Laga M. Heterosexual transmission of HIV. AIDS 1988; 2: S49-S56.
49. Mann JM. Heterosexual transmission of HIV: a global view a decade later. *Int J STD AIDS* 1993; 4: 353-6.
50. N'Galy B, Ryder RW. Epidemiology of HIV infection in Africa. *J Acquir Immune Defic Syndr* 1988; 1: 551-8.
51. Heyward WL, Osmanov S, Esparza J. Establishment of WHO-sponsored sites for HIV vaccine evaluation in developing countries. In: Giraldo G, Bolognesi DP, Salvatore M, Beth-Giraldo E, eds. Development and application of vaccines and gene therapy for AIDS. Vol 48 of Antibiotics and Chemotherapy, Basel, Switzerland, Karger AG Press, 1996;139-44.
52. O'Connell JM, Hogg RS, Chan K, Strathdee SA, McLean N, Martindale SL. Willingness to participate and enroll in a phase 3 preventive HIV-1 vaccine trial. *J Acquir Immune Defic Syndr* 2002; 31: 521-8.
53. Hays RB, Kegeles SM. Factors related to the willingness of young gay men to participate in preventive HIV vaccine trials. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; 20: 164-71.
54. Koblin BA, Heagerty P, Sheon A, Buchbinder S, Celum C, Douglas JM. Readiness of high-risk populations in the HIV Network for Prevention Trials to participate in HIV vaccine efficacy trials in the United States. AIDS 1998; 12: 785-93.
55. Celentano DD, Beyrer C, Natpratan C, Eiumtrakul S, Sussman L, Renzullo PO. Willingness to participate in AIDS vaccine trials among high-risk populations in northern Thailand. AIDS 1995; 9: 1079-83.
56. Jenkins RA, Temoshok LR and Virochsiri K. Incentives and h. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; 9: 36-42.
57. Jenkins RA, Torugsa K, Markowitz LE, Mason CJ, Jamroentana V, Brown AE. Willingness to participate in HIV-1 vaccine trials among young Thai men. Sex Transm Infect

2000; 76: 386-92.
58. McGrath JW, George K, Svilar G, Ihler E, Mafigiri D, Kabugo M. Knowledge about vaccine trials and willingness to participate in an HIV/AIDS vaccine study in the Ugandan military. *J Acquir Immune Defic Syndr* 2001; 27: 381-8.
59. Halpern SD, Metzger DS, Berlin JA, Ubel PA. Who will enroll? Predicting participation in a phase II AIDS vaccine trial. *J Acquir Immune Defic Syndr* 2001; 27: 281-8.
60. Maek-A-Nantawat, Pitisuttithum P, Phonrat B, Bussaratid V, Naksrisook S, Peonim W. Evaluation of attitude, risk behavior and expectations among Thai participants in Phase I/II HIV/AIDS vaccine trials. *J Med Assoc Thai* 2003; 86: 299-307.
61. Koblin BA, Avrett S, Taylor PE, Stevens CE. Willingness to participate in HIV-1 vaccine efficacy trials and the effect of media events among gay and bisexual men in New York city: Project ACHIEVE. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; 15: 165-171.
62. Bartholow BN, MacQueen KM, Douglas JM, Buchbinder S, McKirnan D and Judson FN. Assessment of the changing willingness to participate in phase III HIV vaccine trials among men who have sex with men. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997; 16: 108-15.
63. Koblin BA, Holte S, Lenderking B, Heagerty P. Readiness for HIV vaccine trials: changes in willingness and knowledge among high-risk populations in the HIV network for prevention trials. The HIVNET Vaccine Preparedness Study Protocol Team. *J Acquir Immune Defic Syndr* 2000; 24: 451-7.
64. Moodley K, Barnes J, van Rensburg EJ, Myer L. Willingness to participate in South African HIV vaccine trials—concerns of medical professionals in the Western Cape. *S Afr Med J* 2002; 92: 904-6.
65. MacQueen KM, Buchbinder S, Douglas JM, Judson FN, McKirnan DJ, Bartholow B. The decision to enroll in HIV vaccine efficacy trials: concerns elicited from gay men at increased risk for HIV infection. AIDS Res Hum Retroviruses 1994; 10: s261-s264.
66. Strauss RP, Sengupta S, Kegeles S, McLellan E, Metzger D, Eyre S. Willingness to volunteer in future preventive HIV vaccine trials: issues and perspectives from three U.S. communities. *J Acquir Immune Defic Syndr* 2001; 26: 63-71.
67. McGrath JW, Mafigiri D, Kamya M, George K, Senvewo R, Svilar G. Developing AIDS vaccine trials educational programs in Uganda. *J Acquir Immune Defic Syndr* 2001; 26: 176-81.
68. Scheer S, Douglas JM, Jr., Vittinghoff E, Bartholow BN, McKirnan D, Judson FN. Feasibility and suitability of targeting young gay men for HIV vaccine efficacy trials. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; 20: 172-8.
69. Perisse AR, Schechter M, Moreira RI, do Lago RF, Santoro-Lopes G, Harrison LH. Willingness to participate in HIV vaccine trials among men who have sex with men in Rio de Janeiro, Brazil. Projeto Praca Onze Study Group. *J Acquir Immune Defic Syndr* 2000; 25: 459-63.
70. Grady C. HIV preventive vaccine research: selected ethical issues. *J Med Philos* 1994; 19: 595-612.
71. Gagnon MP, Godin G. Young adults and HIV vaccine: determinants of the intention of getting immunized. Can *J Public Health* 2000; 91: 432-4.
72. Ijsselmuiden CB, Faden RR. Research and informed consent in Africa - another look. N Eng J Med 1992; 326: 830-833.
73. Mariner KW. Taking informed consent seriously in global HIV vaccine research. *J Acquir Immune Defic Syndr* 2003; 32: 117-122.
74. Oliver S. Informed consent and transcultural research. *SAMJ* 1995; 85: 984-985.
75. Woody GE, Metzger D, Mulvaney F. Preparations for AIDS vaccine trials. Recruitment and retention of in- and out-of-treatment injection drug users. AIDS Res Hum Retroviruses 1994; 10: s197-s199.
76. Nelson KE, Beyrer C, Natpratan C, Eiumtrakul S, Celentano DD, Khamboonruang C. Preparatory studies for possible HIV vaccine trials in northern Thailand. AIDS Res Hum Retroviruses 1994; 10: s243-s246.
77. Jackson JB, Musoke P, Fleming T, Guay LA, Bagenda D, Allen M, Nakabiito C, Sherman J, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. Lancet 2003; 362: 859-68.
78. Baeten JM, Richardson BA, Martin HL, Jr., Nyange PM, Lavreys L, Ngugi EN. Trends in HIV-1 incidence in a cohort of prostitutes in Kenya: implications for HIV-1 vaccine efficacy trials. J Acquir Immune Defic Syndr 2000; 24: 458-64.
79. Brown-Peterside P, Rivera E, Lucy D, Slaughter I, Ren L, Chiasson MA. Retaining hard-to-reach women in HIV prevention and vaccine trials: Project ACHIEVE. *Am J Public Health* 2001; 91: 1377-9.
80. Marmor M, Titus S, Wolfe H, Krasinski K, Maslansky R, Simberkoff M. Preparations for AIDS vaccine trials. Retention, behavior change, and HIV-seroconversion among injecting drug users (IDUs) and sexual partners of IDUs. AIDS Res Hum Retroviruses 1994; 10: s207-s213.
81. Bakari M, Lyamuya E, Mugusi F, Aris E, Chale S, Magao P. The prevalence and incidence of HIV-1 infection and syphilis in a cohort of police officers in Dar es Salaam, Tanzania: a potential population for HIV vaccine trials. AIDS 2000; 14: 313-20.
82. Deschamps MM, Johnson WD, Jr and Pape JW. Feasibility and cohort development for HIV vaccine trials in Haiti. AIDS Res Hum Retroviruses 1994; 10: s231-s233.
83. Douglas JM, Judson FN, Parks JP, Buchbinder S and McKirnan D. Participation of homosexual/bisexual men in preventive HIV vaccine trials: baseline attitudes and concerns and predicted behaviors during trials. AIDS Res Hum Retroviruses 1994; 10: s257-s260.
84. Jackson DJ, Martin HL, Bwayo JJ, Nyange PM, Rakwar JP, Kashonga F. Acceptability of HIV vaccine trials in high-risk heterosexual cohorts in Mombasa, Kenya. AIDS 1995; 9: 1279-

83.
85. Myer L, Mathews C, Little F. Condom use and sexual behaviors among individuals procuring free male condoms in South Africa: a prospective study. Sex Transm Dis 2002; 29: 239-41.
86. Weinhardt LS, Forsyth AD, Cary MP, Jaworski BC, Durant LE. Reliability and validity of self-report measures of HIV-related sexual behaviour: Progress since 1990 and recommendations for research and practice. Arc Sex Beh 1998; 27: 155-181.
87. McKirnan DJ, Doetsch J, Vanable P, Buchbinder S, Douglas JM and Judson F. Preparations for AIDS vaccine trials. Developing brief valid screening instruments for HIV-related sexual risk behavior among gay and bisexual men. AIDS Res Hum Retroviruses 1994; 10: s285-s288.
88. Aquilino WS. Privacy effects on self-reported drug-use: interactions with survey mode and respondents characteristics. NIDA research monograph 1997; 167: 383-415.
89. Bloom DE. Technology, experimentation, and the quality of survey data. Science 1998; 98: 867-73.
90. Catania JA. A framework for conceptualising reporting bias and its antecendents in interviews assessing human sexuality. *J Sex Res* 1999; 36: 25-38.
91. Des Jarlais DC, Paone D, Milliken J, Turner CF, Miller H, Gribble J. Audio-computer interviewing to measure risk behaviour for HIV among injecting drug users: a quasi-randomised trial. Lancet 1999; 353: 1657-61.
92. Gribble JN, Miller HG, Rogers SM and Turner CF. Interview mode and measurement of sexual behaviours: Methodological issues. *J Sex Res* 1990; 26: 16-23.
93. Catania JA, Gibson DR, Chitwood DD, Coates TJ. Methodological problems in AIDS behavioural research: influences on measurement error and participation bias in studies of sexual behaviour. Psych Bull 1990; 108: 339-362.
94. Turner CF, Ku L, Rogers SM, Lindberg LD, Pleck JH, Sonenstein FL. Adolescent Sexual Behavior, Drug Use, and Violence: Increased Reporting with Computer Survey Technology. Science 1998; 280: 867-73.
95. Cooley PC, Rogers SM, Turner CF, Al Tayyib AA, Willis G, Ganapathi L. Using touch screen audio-CASI to obtain data on sensitive topics. Computers in Human Behavior 2001; 17: 285-93.
96. Van de Wijgert J, Padian N, Shiboski S, Turner C. Is audio computer-assisted self-interviewing a feasible method of surveying in Zimbabwe? *Int J Epidemiol* 2000; 29: 885-90.
97. Johnson AM, Copas AJ, Erens B, Mandalia S, Fenton K, Korovessis C. Effect of computer-assisted self-interviews on reporting of sexual HIV risk behaviours in a general population sample: a methodological experiment. AIDS 2001; 15: 111-5.
98. Des Jarlais DC, Paone D, Milliken J, Turner CF, Miller H, Gribble J. Audio-computer interviewing to measure risk behaviour for HIV among injecting drug users: a quasi-randomised trial. Lancet 1999; 353: 1657-61.
99. Williams ML, Freeman RC, Bowen AM, Zhao Z, Elwood WN, Gordon C. A comparison of the reliability of self-reported drug use and sexual behaviors using computer-assisted versus face-to-face interviewing. AIDS Educ Prev 2000; 12: 199-213.
100. Jennings TE, Lucenko BA, Malow RM, Devieux JG. Audio-CASI vs interview method of administration of an HIV/STD risk of exposure screening instrument for teenagers. *Int J STD AIDS* 2002; 13: 781-4.
101. Gallant M, Maticka-Tyndale E. School-based HIV prevention programmes for African youth. Soc Sci Med 2004; 58: 1337-51.
102. Jegede AS, Odumosu O. Gender and health analysis of sexual behaviour in south-western Nigeria. *Afr J Reprod Health* 2003; 7:63-70.
103. Musoke D. Another condom uproar in Uganda. New Afr 1991; 37.
104. Dare OO, Cleland JG. Reliability and validity of survey data on sexual behaviour. Health Transit Rev 1994; 4: 93-110.