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Informed consent to participation in preventive HIV vaccine efficacy trials in the light of section 12(2)(c) of the South African Constitution*

Abstract

Clinical trials to develop an effective vaccine against HIV are currently underway in South Africa. The scientific, epidemiologic and socio-economic backgrounds against which these trials are likely to take place are described, as well as the risks and benefits attaching to participation. It is argued that, against this background, informed consent will be difficult to achieve. In the light of this reality, the extent of the constitutional guarantee in section 12(2)(c) is investigated. The content of section 12(2)(c) is analysed, and recent case law that deals with section 12 is examined critically. It is concluded that the constitutional guarantee contained in section 12(2)(c) is an important buttress against communities' exploitation during HIV vaccine trials.

Opsomming

Ingeligte toestemming tot deelname aan voorkomende MIV-entstof proewe in die lig van artikel 12(2)(c) van die Suid-Afrikaanse Grondwet

Kliniese proewe word tans in Suid-Afrika onderneem om 'n effektiewe entstof teen MIV-infeksie te ontwikkel. Die wetenskaplike, epidemiologiese en sosio-ekonomiese agtergronde van hierdie proewe word omskryf, asook die risiko's en voordele verbonde aan deelname. Daar word aangevoer dat ingeligte toestemming teen hierdie agtergrond moeilik haalbaar sal wees, en in die lig hiervan word die omvang van die grondwetlike waarborg in artikel 12(2)(c) ondersoek. Die inhoud van artikel 12(2)(c) word ontleed, en onlangse regspraak betreffende artikel 12 word krities beskou. Daar word bevind dat die grondwetlike waarborg in artikel 12(2)(c) 'n belangrike skans teen die uitbuiting van gemeenskappe tydens MIV-entstof proewe is.

* This article draws upon sections of the author's LLD thesis "Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa" (University of Pretoria 2007).

1. Introduction

Despite their initial optimism, scientists admit that the possibility of developing a cure for AIDS within the next decade remains remote. Although education and information programmes aimed at reducing the HIV infection rate are in place, these have had only limited success.¹ Hence, as with many viral diseases, such as smallpox and poliomyelitis, the development of an effective vaccine offers the only real hope of halting or slowing the HIV and AIDS epidemic.

Phase II clinical trials which have the purpose of establishing the efficacy of various candidate vaccines against HIV are underway in South Africa, and Phase III trials will start in the near future. By definition, these trials involve human subjects. Thus, it is crucial that the existing ethical and legal frameworks for the protection of research participants be examined critically. As Charles McCarthy observes: "We must develop ethical and legal answers that are as sophisticated as the science that develop the vaccine itself".²

This article examines the informed consent of clinical trial participants to their participation in preventive HIV vaccine trials in the light of section 12(2)(c) of the South African Constitution. The constitutional guarantee, however, is but one of a number of sources — albeit an important one — of informed consent law in South Africa and it cannot be seen in isolation from the wider relevance of informed consent in South African ethical guidelines,³ common law, case law and statutes.⁴ However, the liability of a researcher who undertakes preventive HIV-related clinical research without the research participant's informed consent, based not upon the Constitution, but upon the South African common law, case law and legislation, is the subject of an earlier article, and is therefore not revisited here.⁵

The article is structured as follows: the scientific and epidemiological risks inherent in HIV vaccine trial participation are raised within the South African socio-economic context. The aim here is to establish whether potential preventive HIV vaccine trial participants are vulnerable to exploitation. Next, the extent of the constitutional guarantee in section 12(2)(c) is examined, and recent case law which deals with section 12(2)(c) is analysed. Finally, conclusions are drawn and recommendations are made.

1 Such as the ABC campaign in Uganda.

2 McCarthy cited in Weisburd 1987:329.

3 Various ethical guidelines on informed consent to participation in clinical research exist in South Africa, but will not be discussed here. In this regard, see van Wyk: 2001:3.

4 In *Pharmaceutical Manufacturers Association of South Africa In re: Ex Parte Application of the President of the Republic of South Africa* 2000 (3) BCLR 241 (CC) the Constitutional Court observes that:

"[t]here are not two systems of law, each dealing with the same subject matter, each having similar requirements, each operating in its own field with its own highest court. There is only one system of law. It is shaped by the Constitution which is the supreme law, and all law, including the common law, derives from the Constitution and is subject to constitutional control" (para 44).

5 See Nienaber 2008:forthcoming.

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A number of articles deal with adolescent HIV vaccine trial participation in the light of new statistics⁶ showing the increasing incidence of HIV infection in that age group.⁷ They investigate the implications of the new *National Health Act*,⁸ the Constitution and local and international ethical guidelines upon adolescents' vaccine trial participation and the notion of informed consent. By contrast, this article focuses on informed consent with respect to adults; the problems presented by adolescent participation are not discussed.

The article has a very specific focus — informed consent to participation in preventive or non-therapeutic⁹ HIV vaccine efficacy trials in the light of section 12(2)(c) of the Constitution. As a consequence, the discussion on informed consent is limited to a discussion of the law as it pertains to competent¹⁰ adult¹¹ persons participating in non-therapeutic HIV vaccine trials (and therefore not research to find a curative vaccine for HIV, or so-called pure 'therapeutic'¹² vaccine research); and the discussion pertains to controlled clinical trials and not to standard medical interventions or treatment.

2. The preventive HIV vaccine efficacy trial context

2.1 Epidemiologic and scientific contexts

Sub-Saharan Africa is, by far, the region that is the worst affected by the HIV and AIDS epidemics. Two-thirds or 66.6% of all adults and children with HIV globally live in sub-Saharan Africa, amounting to almost 25 million people.¹³ Also, 2.1 million Africans died of AIDS in 2006, totalling almost three quarters or 72% of all AIDS deaths globally.¹⁴ Within sub-Saharan Africa, southern Africa is the worst off — one-third or 32% of all people living with the virus are in southern Africa and 34% of all AIDS deaths in 2006 occurred in southern Africa.¹⁵

6 See HSRC 2005:37.

7 See eg Van Wyk 2005:35; Strode *et al* 2005:225; Slack and Kruger 2005:269; Slack *et al* 2005:682. On the scientific justification for adolescent participation, see Jaspán *et al* 2005:785.

8 Act 61/2003.

9 'Non-therapeutic' research aims to 'benefit people other than the research participant ... [t]he acquisition of knowledge may be of no immediate benefit to the participant or healthy volunteer' MRC 2004:para 2.1.2.2.

10 In the light of current ethical, legal and constitutional provisions, non-therapeutic HIV-related clinical trials are unlikely to be undertaken on incompetent or mentally incapacitated persons. Regarding research on mentally incompetent persons, see eg Van Staden 2007:10.

11 As pointed out above, a discussion of the participation of children in HIV vaccine efficacy trials falls outside the scope of this article. For more on the participation of children in HIV-related clinical research, specifically HIV vaccine research, see the sources referred to in fn 7.

12 The aim of 'therapeutic' research is 'to benefit the individual research participant or patient by treating or curing their condition' MRC:para 2.1.2.1.

13 UNAIDS 2006:6.

14 UNAIDS 2006:6.

15 UNAIDS 2006:3.

Within southern Africa, South Africa is experiencing one of the most devastating epidemics. A total of 5.5 million people in South Africa were living with the virus by the end of 2005 — the highest number of individuals infected by HIV in any single country in the world.¹⁶ The level of HIV among women attending antenatal clinics in South Africa is at its highest yet — 30.2 per cent.¹⁷

Even though the Human Sciences Research Council's *South African national HIV prevalence, HIV incidence, behaviour and communication survey 2005* puts South Africa's overall HIV prevalence rate lower than that estimated by UNAIDS, these percentages are still alarming.¹⁸ In three provinces (the Eastern Cape, Free State and KwaZulu-Natal) the average life expectancy has fallen below 50 years.¹⁹ In this context, and given the fact that alternatives such as microbicides and male circumcision do not presently provide a sustainable solution, it is imperative that a vaccine that curbs the spread of HIV is found.²⁰

A successful preventive HIV vaccine should be effective, safe and affordable.²¹ But what is an 'effective' vaccine and how is effectiveness measured? In response to these questions, the following goals or endpoints for preventive HIV vaccine development in South Africa have been outlined by vaccine scientists:²² a preventive HIV vaccine will be considered successful if it succeeds either in preventing infection (known as sterilising immunity), or preventing disease.²³ If neither of the above is possible, a third possibility is that the successful vaccine will slow down or delay the progression of the disease from infection to death.²⁴

16 UNAIDS 2006:11.

17 As above; based on statistics supplied by the Department of Health, South Africa, 2006.

18 HSRC 2005:21-41. Different HIV prevalence studies yield different results. In 2004, the Department of Health published the National HIV and Syphilis antenatal seroprevalence survey, which, based on a sample of 16 061 women at antenatal clinics across the country. This survey estimated that in 2004, 29.5% of pregnant women in South Africa were HIV positive and that a total of 6.29 million South Africans were living with HIV. The HSRC's survey, however, estimates that a lower total, 24.4%, were living with HIV. This lower estimate may be due to the different methodologies used by the two surveys.

19 UNAIDS 2006:11.

20 See Nienaber 2008:para 1 for arguments on why a preventive HIV vaccine is necessary, eg viral resistance to HAART, its toxicity, poor drug compliance and the lack of effective alternative methods. Also see Janse Van Rensburg 2002:577-579.

21 Janse Van Rensburg 2002:577; Weidle *et al* 2002:2264; Schoub 2002:561.

22 Weidle *et al* 2002:2264; Schoub 2002:561.

The endpoint of a therapeutic HIV vaccine trial is that the vaccine succeeds in ameliorating the disease by eliciting an immune response in the infected person (see Janse Van Rensburg 2002:580; Schoub 2002:561).

23 For most infectious diseases, sterilising immunity is the vaccine endpoint. In the case of sterilising immunity, the body is able totally to eliminate the virus, infection is thus prevented, and there are no signs and symptoms of the disease. Many scientists believe that it is not possible to develop an HIV vaccine that will prevent infection (see Janse Van Rensburg 2002:579; Weidle *et al* 2002:2264; Schoub 2002:561; Van Harmelen and Williamson 2000:569-570). Once a person is infected with HIV, the virus remains in that person's body, as it integrates itself into the person's DNA.

24 Janse Van Rensburg 2002:579; Weidle *et al* 2002:2264; Schoub 2002:561. The asymptomatic period of the disease will be prolonged, and there will be no or few symptoms (Janse Van Resburg 2002:579-580).

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In other words, the vaccine will succeed in lowering the viral load in the blood of infected persons for a considerable period of time. This third possibility will indirectly decrease the transmission of the disease;²⁵ the vaccine thus will have a limited effect on the health of the vaccinated person (as she will become ill eventually), but a potentially significant effect on the epidemiology of HIV within the community.²⁶

Vaccine efficacy is measured during Phase II and III vaccine trials.²⁷ Phase III vaccine efficacy trials are large-scale, double blind,²⁸ placebo-controlled,²⁹ randomised³⁰ clinical trials. Efficacy is measured statistically, but amounts to a situation in which those participants who received the HIV preventive vaccine have a significantly lower incidence of HIV infection than those receiving the placebo.³¹

25 A high viral load is a risk factor for HIV transmission.

26 This is known as a 'surrogate endpoint', Janse Van Rensburg 2002:579; Weidle *et al*/2002:2264; Schoub 2002:561. As a high viral load is a risk factor for HIV, a lower viral load will lead to fewer HIV infections in the community, which in turn will lead to a slower spread of the disease within that community.

27 Phase I vaccine trials are the first introduction of the study drug into humans and are aimed at determining levels of toxicity, the appropriate dosage and its safety. Drug dynamic and absorption studies are performed during this phase. Furthermore, usually no control group is included and only a limited number of participants are enrolled — from as few as 10 to about 100 (Levine 1986:5-6; Rick 2004:145).

Phase II vaccine trials are controlled clinical trials to ascertain the effectiveness and relative safety of the developmental vaccine and participants are randomised to a control group or an active group (Levine 1986:6; Rick 2004:145).

Phase III vaccine trials are large-scale trials, usually including thousands of participants, which aim at establishing the efficacy of the vaccine and the possibility of the existence of adverse effects, and use the safe, effective dosage and administration schedule determined by the preceding phases (Levine 1986:6-7; Rick 2004:145).

28 The fact that the trial is often "blinded", tries to exclude observer or participant bias. In a "double blind" trial, neither the researcher nor the participant knows who is given the "real" intervention and who is receiving the dummy or placebo. A principle investigator wishing the trial drug to be proven effective may actively (and even subconsciously) select participants who stand a better chance of benefiting from the experimental regimen and ensure that those participants are part of the 'experimental' group; trial participants who know that a new drug is being tested on them may feel an 'improvement' in their condition which may be absent as they are part of a placebo group (Levine 1986:185-186).

29 Research participants receiving the existing (standard) drug or a placebo are referred to as the control group, while the participants receiving the new treatment are referred to as the experimental group. A placebo-controlled trial, therefore, is one which includes a control group which receives the standard treatment or placebo (Foster 2001:22).

30 The "randomised" controlled clinical trial is the most widely used (experimental) research method and is used to compare the efficacy and safety of two or more interventions or regimes. Randomisation is the practice of allocating participants to different experimental groups by random selection. In this way researchers attempt to control for any chance of an outside (non-experimental) factor influencing the results of the trial (see Levine 1986:185; Forster 2001:22).

31 What is considered to be "statistically lower" is a matter for debate. VaxGen's recently completed vaccine trials in Thailand and the USA were looking at a reduction in the level of HIV infection by at least 30% at a statistically significant level. This means that an efficacy of more than 30% would be seen 95 times out of 100 (Farham 2006:3).

During a Phase III efficacy trial, the possibility of adverse effects is also examined.³² Large numbers of volunteers take part, usually more than a thousand.³³ As the efficacy of the candidate vaccine needs to be established, these volunteers should be at high risk for infection, and are drawn from communities with a high incidence of HIV.³⁴

Abdool Karim outlines the factors at play in the selection of an ideal HIV vaccine trial site and its environment.³⁵ They are:³⁶

- an epidemiological situation with HIV incidence data on high-risk groups and evidence of high cohort retention rates over trials spanning three to five years (in everyday language this translates to a sufficiently large number of high-risk HIV-negative individuals who can be enrolled and followed up for three to five years);
- an adequate clinical infrastructure (which includes facilities for counselling, the management and storing of the vaccine, facilities for data management and good laboratory management);
- investigators experienced in clinical research and clinical trial methodology and management; and
- the availability of an adequate cohort management, clinical and laboratory infrastructure.

In South Africa, there are currently four preventive HIV vaccines being tested in humans, namely:³⁷

32 Abdool Karim 2002:589.

33 The VaxGen Phase III preventive HIV vaccine efficacy trial involved 5009 volunteers.

34 In communities with a low HIV incidence rate, many more participants have to be enrolled in the trial in order to achieve statistical validity. Such trials are necessarily more expensive.

35 Abdool Karim 2002:589.

36 Abdool Karim 2002:589.

37 Adapted from AVAC 2006:21-25. These tables do not account for vaccines presently in pre-clinical testing.

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PROT #	Start date	Sponsor, funder, developer	Trial site(s)	Vaccine	# PRTCP	CLADE
HVTN 059 (Phase I)	Oct 2004	HVTN, SAAVI, Alphavax	US, South Africa, Botswana	VEE (Venezuelan equine encephalitis) vector with gag	96	C
HVTN 050/ MERC 018 (Phase I)	Jan 2004	NIAID, HVTN, Merck	Thailand, Brazil, Haiti, Puerto Rico, South Africa, US, Malawi, Peru	Adenovirus vector with gag	435	B
IAVI A002 (Phase II)	Nov 2005	Children's Hospital of Pennsylvania, Columbus Children's Research Center, Indian Council of Medical Research, National AIDS Control Org, Targeted Genetics Corporation	South Africa, Uganda, Zambia	AAV2 (adeno-associated virus type 2) vector with gag, pol, AERT	91	C
HVTN 204 (Phase II)	Sept 2005	DAIDS, HVTN, VRC, Vical, GenVec	US, Brazil, South Africa, Haiti, Jamaica	Prime: DNA vaccine with gag, pol, nef + env Boost: Adenovirus vector with gag, pol + env	480	B A, B, C

No Phase III preventive HIV efficacy trials are presently taking place in South Africa, but the two candidate vaccines in Phase II, protocols IAVA A002 and HVTN 204, are likely to enter Phase III trials in the near future, should the results of their Phase II trials be satisfactory. Pre-clinical testing is also ongoing.³⁸

The product by AlphaVax, protocol HVTN 059, was the first candidate vaccine to be approved by the MRC for testing in humans.³⁹ The vaccine utilises virus-like particles, containing parts of an attenuated strain of Venezuelan equine encephalitis (VEE) virus and a gene from a South African strain of the HIV virus (*gag*), to deliver the vaccine to the immune system.⁴⁰

Clinical trials of the AlphaVax vaccine are taking place at two clinical trial sites in South Africa — the Perinatal HIV Research Unit at the Chris Hani Baragwanath Hospital in Soweto and the SAAVI Vaccine Research Unit at the Medical Research Council in Durban.⁴¹ In the USA, trial sites are Johns Hopkins University, Columbia University, the University of Rochester and Vanderbilt University.⁴²

All four vaccines being tested are live vector vaccines; in other words, they are using live bacteria or viruses, thought harmless to humans, to transport specific HIV genes that introduce HIV proteins into the body. These genes are the *gag*, *pol*, *env*, *AERT* and *nef* genes indicated in the fifth columns of the tables above. Also, the South African HIV-1 epidemic is predominantly of clade C, and therefore this clade is used in the vaccines that are tested in South Africa (with the exception of the HVTN 204 trial, which is an inter-clade vaccine trial).⁴³

One vaccine, the one being tested in protocol HVTN 024, is a prime-boost vaccine, where a DNA vaccine (DNA vaccines are direct injections of genes coding for specific HIV proteins — in this case *gag*, *pol*, *nef* + *env*)⁴⁴ plus a boost is given; in this case an Adenovirus vector with *gag*, *pol* + *env* proteins.

Each of the four vaccines in the clinical trials in South Africa is the product of a partnership between the public and private sectors.⁴⁵ This is due to the fact that vaccines tend to be less commercially viable or successful than other

38 See SAAVI 2006:1, 7-9 for a list of vaccine products by the South African AIDS Vaccine Initiative (SAAVI) currently in preclinical testing in South Africa; eg, the University of Cape Town has a number of DNA vaccines and a recombinant modified vaccinia Ankara vaccine that are almost ready for clinical testing. See also Williamson 2002:207-208.

39 SAAVI 2003:1.

40 SAAVI 2003:1. As the vaccine consists of only a small section of genetic material from HIV, and does not include all the genetic elements needed to reconstitute live HIV, scientists believe that there is no possibility of the vaccine itself causing HIV infection. However, compare concerns about the safety of using a VEE vector (see Veljkovic *et al* 2003:3528 and Veljkovic *et al* 2004:465).

41 SAAVI 2003:1.

42 SAAVI 2003:1. There are 48 trial participants in the US, and 48 in South Africa.

43 The trial product contains viral material from clades A, B and C.

44 When the DNA is injected, the encoded viral proteins are produced, just as with live vectors (NIAID, NIH 2003: 5).

45 See 3rd column under 'sponsor', 'developer', 'funder'.

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treatments, and, for this reason, are a greater financial risk to pharmaceutical companies — “vaccine research and development requires expenditures that are substantial, long term and relatively high-risk”.⁴⁶ It is estimated that the average cost of developing a new human vaccine is around \$US250 million.⁴⁷ A HIV vaccine is estimated to cost much more.⁴⁸

It is at this point perhaps necessary to again remember the vitally important distinction between *preventive* HIV vaccine efficacy trials and other (therapeutic) HIV drug research, or even *therapeutic* HIV vaccine efficacy trials. In the case of HIV-drug or therapeutic research, or research aimed at finding a therapeutic vaccine,⁴⁹ clinical trial participants are necessarily HIV positive. As the clinical trial is aimed at studying the effect of the therapy on the individual, and on the progression of the disease, only those who are suffering from the disease may be enrolled in clinical trials. However, in the search for an effective *preventive* HIV vaccine, HIV negative trial participants are used to test the candidate vaccine.

This makes preventive HIV vaccine trials such a special case: otherwise healthy volunteers are inoculated with (attenuated) HIV. While this necessarily is done in all preventive vaccine research, on the whole other vaccine research deals with diseases less deadly.⁵⁰ In the case of preventive HIV vaccine trials, the infection (should it materialise) has no cure.

At present it is not foreseen that HIV researchers will soon undertake clinical trials in humans using live⁵¹ virus material but, as relatively little is known about the virus and the body’s immune reaction to it and considering that candidate vaccines will be tested in healthy volunteers, the legal and ethical implications of such trials are far-reaching.

A guiding principle that all human subject research has to comply with in order to be considered ethical and legal is that there should be a favourable balance between risk and potential benefit. Numerous writers have outlined the risks and benefits inherent in HIV vaccine trial participation.⁵² For the sake of completeness, these risks are summarised below. The benefits of participation are outlined later.

46 Ruff 2002:127.

47 World Health Organisation ‘The World Health Report — 1998’, cited in Ruff 2002:127. Vaccines are expensive to develop; the Global HIV Vaccine Enterprise estimates that US\$1.1-US\$1.2 billion is needed annually to speed the search for a safe, effective HIV vaccine (see AVAC 2006:19).

48 AVAC 2006:19.

49 This is given to HIV-positive persons, so that the vaccine will ‘teach’ the body’s own immune system to fight the disease, prolonging (perhaps indefinitely) the asymptomatic phase of the disease.

50 Measles, rubella, mumps.

51 As their name indicates live (attenuated) viruses are ‘alive’ and able to replicate in the vaccinated person (Mackett and Williamson 1995:121; Rick 2004:78; Nicklin *et al* 1999:318; Klein and Ho 2000:307).

52 See eg UNAIDS 2000:28; Graham and Wright 2003:1335; Slack *et al* 2000:293.

2.1.1 Risks borne by participants

At the outset it should be remembered that the risks of HIV preventive vaccine efficacy trials differ according to vaccine design and trial design. Some vaccines are safer than others⁵³ and the social and health status of the individual taking part in the trial also may contribute to the probability and magnitude of the risk.

Risks borne by participants of HIV preventive vaccine efficacy trials are physical, psychological and social in nature. It must be remembered that, as no large-scale Phase III trials have yet been undertaken in South Africa, only an estimate of the problems that are likely to be encountered can be presented, based on experience gained from Phase I and II trials, here and abroad.⁵⁴

- Adverse autoimmune reactions to the vaccine and the worsening of established infections

Participation in HIV preventive vaccine efficacy trials expose participants to the risk of adverse autoimmune reactions to the vaccine and the possibility that the participant will suffer from a worse infection should she ever become infected with HIV.⁵⁵

Fears with regard to adverse autoimmune reactions relate to the fact that HIV's gp160 contains several regions (such as HLA-DR and interleukin-2) with sequences homologous to that of cellular proteins (especially those found on human CD4 cells).⁵⁶ It is feared that vaccination will stimulate autoimmune reactions against the body's own CD4 cells.⁵⁷ This theory is borne out by the fact that HIV-infected persons show a high incidence of autoimmune reactions.⁵⁸

The possibility that HIV vaccination could worsen illness, if the trial participant should be infected with HIV subsequent to vaccination, has been mentioned as a possible risk to participation.⁵⁹ To date this risk has not materialised, although there is some evidence that this is the case *in vitro*.⁶⁰ Further, with regard to this risk there is the possibility that a trial participant may have a greater risk of developing an established infection upon being exposed to HIV than others.⁶¹

Someone already infected with HIV, when vaccinated, may develop a more serious and worse infection.⁶² This may happen in cases where the participant is in the early stages of infection before sufficient antibodies are produced to

53 See Nienaber 2007:53-57.

54 For more on risks that have indeed materialised during VaxGen's recently-completed vaccine trial, see eg Francis *et al* 2003:147 and Coletti *et al* 2003:161.

55 Graham and Wright 2003:1335.

56 Graham and Wright 2003:1335.

57 Graham and Wright 2003:1335.

58 Graham and Wright 2003:1335. So far, low levels of CD4-antibodies have indeed been detected in vaccine trial participants (see eg Keay *et al* 1992:1091). See also the commentary on the article by Veljkovic *et al* below.

59 Graham and Wright 2003:1335.

60 Graham and Wright 2003:1335.

61 UNAIDS 2000:28.

62 Slack *et al* 2000:293.

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show up on standard ELISA assays. The person is diagnosed as HIV negative, whereas, in fact, she is HIV positive, and then inoculated.⁶³

- Adverse reactions to the vaccine itself

Other physical risks to HIV vaccination are adverse reactions to the vaccine itself,⁶⁴ pain, skin irritations, fever, and malaise.⁶⁵ HIV vaccination may require repeated inoculations, each in turn producing these adverse effects.

- Live vaccines

Live vaccines carry the risk that the vaccine virus may mutate sufficiently to revert back to its virulent form and produce HIV infection. Although pre-clinical research is being done on live vaccines, there is no indication that these vaccines will be tested on humans at present. Should this occur, however, trial participants would be exposed to even more serious risk of harm.

- Immune tolerance

Participation in a preventive HIV vaccine efficacy trial may result in immune tolerance which, in turn, will prevent the trial participant from being successfully immunised against HIV in the future.⁶⁶ This is a potentially serious risk, as it might mean that the participant will not be able to be given a subsequent, more effective vaccine.⁶⁷

- Stress, anxiety and depression

Psychological risks to participants in HIV preventive vaccine efficacy trials include stress, anxiety and depression due to having to discuss intimate sexual matters with trial administrators, and the stress inherent in being subjected to repeat HIV testing.⁶⁸

- Sexual relationships may become strained

Participation in HIV preventive vaccine efficacy trials might cause strain in the participant's sexual relations with others, especially when the participant's sexual partner (mistakenly) believes that the participant can infect others with the virus.⁶⁹

63 This risk may be overcome by the utilisation of new testing technologies. Some newer tests, such as those employed by the South African Blood Transfusion Services, are able to detect infection with HIV much earlier than standard ELISA tests.

64 Such as an allergic reaction to one of its components.

65 UNAIDS 2000:28.

66 Slack *et al* 2000:293.

67 Slack *et al* 2000:293.

68 UNAIDS 2000:29.

69 UNAIDS 2000:29.

The realisation of this particular risk has potentially far-reaching consequences for the trial participant: a misinformed sexual partner may even end his or relationship with the participant. The informed consent process should, therefore, include information on this potentially serious complication of participation.

- Increased risk-taking behaviour

Another potential risk of participating in HIV preventive vaccine efficacy trials is increased risk-taking behaviour by trial participants, caused by an (erroneous) belief that the candidate vaccine will protect them from infection.⁷⁰ This belief may be particularly dangerous in cases where trial participants belong to the placebo group.⁷¹

- Cultural isolation

Trial participants from another culture and belief system who are exposed to alien scientific concepts may experience stress and anxiety.⁷²

- False-positive HIV test results

After being vaccinated, participants will test HIV-positive on standard ELISA assays even though they are not infected with HIV. This could have serious consequences for participants' prospects of successfully taking out insurance, finding employment, and so on. Some writers have rejected these fears of discrimination based on positive HIV antibody tests. Their argument is that a standard immunoblot can easily discriminate real HIV infection (which should show antibodies to all HIV's proteins) from vaccine-induced HIV antibodies (to the envelope proteins alone).⁷³ However, as vaccine science progresses and vaccine designs become more complex, it is unlikely that immunity produced by the more complex DNA or vector vaccines will be easily distinguishable in antibody laboratory tests from real HIV infection.⁷⁴

- Negative perceptions and stigmatisation

Not only will HIV preventive vaccine efficacy trial participants test positive on standard HIV-antibody tests, but they may be perceived by a misinformed public to *be* HIV positive. Participants in Phase III trials are usually high-risk individuals and this perception may cause them to be stigmatised and discriminated against. The communities from which these participants are drawn may be similarly stigmatised.

It is difficult to evaluate the seriousness of the risks mentioned above if one is not an expert in vaccine science; physical risks attendant upon HIV trial participation are especially difficult to assess. Nor is it easy to accurately estimate the chance of these risks materialising.

Although many vaccine scientists are quick to allay fears concerning the safety of vaccines, others are not so hasty, stressing the risks outlined above. For example, well respected virologists Veljkovic *et al*⁷⁵ raise serious concerns about preventive HIV vaccine safety.

70 See Celentano *et al* 1995:1079.

71 This is why the consent process should, of necessity, stress the possibility that the participant could be part of a placebo-group, receiving no active vaccine, and therefore at risk of infection.

72 UNAIDS 2000:29.

73 Francis *et al* 2003:151.

74 Francis *et al* 2003:151.

75 Veljkovic *et al* 2004:465-486.

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Veljkovic *et al* draw attention to the fact that, initially, the AIDS Research Advisory Committee in the USA commented in their report (about Phase III HIV-1 gp120/160 vaccine trials) that they “should not be conducted at this time in this country”.⁷⁶ This decision not to conduct Phase III efficacy trials was based on the “chance that tested HIV vaccines will compromise the immune system and make the recipient more vulnerable to infection”.⁷⁷ Despite this, “an advisory committee to WHO [...] recommended that large-scale Phase III of these HIV vaccine candidates should be allowed to proceed in developing countries”.⁷⁸ This recommendation was based on the argument that “the desperate situation posed by the AIDS epidemic justifies acceptance of the so-called ‘small risks’ involved”.⁷⁹

When this specific gp120/160 vaccine later proceeded to Phase III trials in Thailand, the initial fears expressed about its safety were proven justified. Researchers reported that the vaccine “acted as a decoy for the immune system ... increasing the likelihood of infection as well as disarming the immune system ... increasing the likelihood of rapid disease progression, which is seen in later-infected vaccines”.⁸⁰

Another widely used vaccine strategy, also criticised by Veljkovic *et al*, is the use of live recombinant vectors to carry vaccine proteins into the human body.⁸¹ Veljkovic *et al* express fears that, when combined with HIV-1 gp 120/160, these recombinant vectors can mutate in the human body to cause dangerous infections.⁸² Even if the probability of that happening is very low, it is not nil, posing a grave risk to HIV vaccine trial participants.⁸³

Veljkovic *et al* further caution against the use of a Venezuelan equine encephalitis (VEE) vector vaccine, such as the one used in the HVTN 059/AlphaVax vaccine tested in South Africa.⁸⁴ Veljkovic *et al* express several reasons for concern about a VEE-based vaccine, not least of which is the fact that, according to reported data, the viral family to which VEE belongs is inherently recombinogenic in nature.⁸⁵

Moreover, Veljkovic *et al* caution against other viral vectors used in vaccines, such as the herpes simplex virus vector,⁸⁶ poxvirus (or vaccinia) vectors⁸⁷ and HIV antigens found in plants.⁸⁸

76 Veljkovic *et al* 2004:466.

77 Veljkovic *et al* 2004:466.

78 Veljkovic *et al* 2004:466.

79 Veljkovic *et al* 2004:466.

80 In this regard, see Locher *et al* 1999:1685.

81 Veljkovic *et al* 2004:467. See also Nienaber 2007:48-62.

82 Veljkovic *et al* 2004:467.

83 Veljkovic *et al* 2004:467.

84 See above.

85 Veljkovic *et al* 2004:472, citing Weaver *et al* 1993:375-390 and Rumenapf *et al* 1995:621-633.

‘Recombinogenic’, as the term indicates, implies an ability to ‘recombine’.

86 Veljkovic *et al* 2004:472.

87 Veljkovic *et al* 2004:473.

88 Veljkovic *et al* 2004:476.

The question that needs to be answered is whether Veljkovic *et al* are being unnecessarily conservative, or even alarmist, advocating caution when everybody else is forging ahead with large-scale preventive HIV trials in high-risk populations, or whether their warnings indicate a real element of danger (however small). At present it is uncertain which of the perils they warn about, or the risks outlined above, if any, will materialise during HIV vaccine efficacy trials in South Africa. However, it is clear that at least some of these risks, potentially, are very serious — and that at least one of the virologists' warnings has manifested in harm to preventive HIV vaccine trial participants.⁸⁹ Inevitably, this example leads to the conclusion that the risks attendant upon preventive HIV vaccine trial participation in South Africa may be more serious than is openly admitted.

2.1.2 Benefits of participation

Risk should be balanced with the potential benefit that may accrue from HIV vaccine trial participation. A “benefit” is defined as follows:⁹⁰

A benefit is the opposite of a harm, and refers to any favourable outcome of the research to society or to the individual. The outcome of research is never certain at the outset, and it is thus proper to consider the probability of benefit as well as its magnitude. In practice, ‘benefit’ often stands for the combined probabilities and magnitudes of several possible favourable outcomes.

Preventive HIV vaccine trial participation has the potential to benefit the individual participant and the community in a number of ways:

- Increased feelings of self-worth because the trial participant is helping others

This is one of the most important benefits derived from participation in non-therapeutic trials (where the participant does not suffer from the disease for which a therapy is being researched). The individual trial participant may not derive any personal benefit from participation, but knows that she is helping to find the answer to a research question, and thus helping to increase knowledge that could benefit others in the future, be they identifiable or non-identifiable.⁹¹

During the VaxGen trial, injection drug users, when asked why they took part, indicated that they wanted to do something to help stop the spread of the HIV epidemic.⁹²

89 As described by authors referred to in fn 58 above.

90 MRC 2002:Guideline 9.12.4.5.

91 They are identifiable if they belong to a specific group, such as pregnant women, new-born babies, and so on. They are unidentifiable if they belong to society in general, such as instances of research aimed at bettering our understanding of the risk factors for contracting a certain disease, research on blood or tissue samples of healthy volunteers, etc.

92 Francis *et al* 2003:153.

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- Increased access to health care and better quality health care

This is an important benefit of participation, especially in resource-poor countries such as those in Africa where little is spent on health care. During preventive HIV vaccine trials, participants will have access to treatment for STIs, general medical examinations, HIV-testing with pre- and post-test counselling, and so forth.⁹³

- Counselling on risk-taking behaviours

Preventive HIV vaccine efficacy trial participants are given extensive counselling to reduce high-risk behaviours which expose them to HIV infection. Initially it was debated that counselling will eliminate risk-taking behaviour totally, rendering the trial worthless, but this expectation has not materialised.⁹⁴

- Increased community awareness of scientific and epidemiological aspects of the HIV virus

Through information campaigns and counselling, communities learn more about vaccine science and disease prevention. Although some communities may be well-informed already on these issues, others will benefit from additional knowledge.

- An efficacious HIV preventive vaccine

Most writers seem to forget the development of an efficacious preventive HIV vaccine as a potential benefit of trial participation. Such a vaccine will not only benefit the trial participant, but society in general. Such a benefit is immeasurable.

The MRC's ethical guidelines instruct us to consider both the "probability of benefit as well as its magnitude". In the case of HIV vaccine efficacy trial participation, the first four benefits mentioned above at least are likely to occur or are "probable". It is probable that individuals and communities taking part in vaccine trials will benefit from increased medical attention, counselling on risk-taking behaviour and an increased knowledge about scientific concepts and knowledge about the epidemiological aspects of HIV.

In the case of the last potential benefit mentioned above, that of finding an effective vaccine for HIV, there is little doubt about the magnitude of the potential benefit. However, one should also consider the probability of the benefit. At best the probability of finding an effective vaccine is unknown at this stage; or worse, unlikely. In the case of an individual trial and an individual participant, such a probability cannot be very great, especially not during earlier trials, as many scientists predict that an effective HIV preventive vaccine is at least ten years in the future.

The above benefits reflect some of the reasons why preventive HIV vaccine trials are going ahead and are attracting participants, despite the precarious

93 Whether trial participants who become HIV positive during a vaccine trial should have access to ARVs for the rest of their lives, is an important and much-debated issue, but lies outside the scope of this article. In this regard, see Tangwa 2001:156; Resnik 2001:11; Barry and Rawarth 2002:57.

94 See eg Francis *et al* 2003:153.

nature of the knowledge so far gained about the possible risks and side-effects of these trials.

An analysis of the socio-economic context of preventive HIV vaccine trials in South Africa is presented below.

2.2 Socio-economic context

This section outlines the socio-economic context in which (specifically Phase III) preventive HIV vaccine efficacy trials are likely to take place in South Africa, highlighting the link between a high risk⁹⁵ of HIV infection and socio-economic factors such as poverty, gender discrimination, detrimental cultural practices and the stigmatisation of people living with the virus, in order to set the stage for a discussion of the implications of such a link for the constitutional guarantee on informed consent in HIV vaccine trials in later paragraphs.

Public health campaigns which proclaim that HIV “knows no boundaries such as wealth, race, colour, gender or social status” are misleading (though, perhaps, not intentionally). Whether a person is at risk for HIV infection depends, not only on whether that person practices safe sex, but, to a certain extent, be it indirectly, on the society and culture in which that person finds him- or herself.⁹⁶

Several studies have shown a correlation between poverty and HIV infection.⁹⁷ Poor people become infected not because they are poor, but because of the structural inequalities pervasive in the societies and cultures in which they live.⁹⁸ Anton Van Niekerk sums up the situation:⁹⁹

Viral diseases, as we know, do not all become epidemics. To become an epidemic, a niche or social context is required. In Africa ... poverty is the main aspect of this niche or social context.

95 ‘Risk’ is used here as an attribute of an environment, not of a group of people. The term is used in popular language to indicate a distinction between those ‘at risk’ and those ‘not at risk’; between ‘us’ and ‘them’.

96 In this regard, see eg Over ‘The Effects of Societal Variables on Urban Rates of HIV infection in Developing Countries: An Exploratory Analysis’ in Ainsworth *et al* 2000:39, who remarks that “social, cultural and economic conditions will influence the frequency of risky sexual behaviour”.

97 See eg Barnett and Whiteside 2002:124-156, 159-181, 182-195; Van Niekerk ‘Moral and social complexities of AIDS in Africa’ in Van Niekerk and Kopelman 2005:53-70; Benatar in Van Niekerk and Kopelman 2005:71-83. Barnett and Whiteside comment: ‘Thus relative wealth reduces vulnerability at all levels from the individual to the nation. These resources are not purely financial; they may include skilled labour, or access to care; even a strong, cohesive and compassionate civil society’ (on 167).

98 There is a correlation — but poverty is not the cause of HIV-infection, it is the economic context in which HIV thrives. President Mbeki (mistakenly) regards poverty as the cause of HIV/AIDS (in this regard, see Van Niekerk ‘Moral and social complexities of AIDS in Africa’ in Van Niekerk and Kopelman 53-54.

99 Van Niekerk in Van Niekerk and Kopelman 2005:55.

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After infection the progression of the disease is an expression of economic and/or social inequality. The rich can afford ARVs, the poor cannot. The rich stay healthy longer because of better access to health care, better nutrition and better living standards. This is not only true for the individual, but also for communities, countries, regions and continents. Judge Edwin Cameron comments as follows upon the situation in 2000, before the roll-out of ARVs in the public sector:¹⁰⁰

I can take these tablets, because on the salary I earn as a judge, I am able to afford their cost ... In this I exist as a living embodiment of the iniquity of drug availability and access in Africa ... My presence here embodies the injustices of AIDS in Africa, because, on a continent in which 290 million Africans survive on less than one US dollar a day, I can afford monthly medication costs of about US \$400 per month. Amidst the poverty of Africa, I stand before you because I am able to purchase health and vigour. I am here because I can afford to pay for life itself.

In the case of women the divide between rich and poor is even more marked: in developed countries, generally, women living with HIV/AIDS are able to stay healthy longer and enjoy a better quality of life. In pregnancy, they have access to Nevirapine and other antiretrovirals which prevent the transfer of HIV to their child. In less developed countries, women on the whole lack access to health care, also to HAART.¹⁰¹ They get ill sooner, and inevitably die of AIDS. In pregnancy, their chances are one in three of passing HIV on to their children: '[t]hus relative wealth reduces vulnerability at all levels from the individual to the nation'.¹⁰²

HIV infection is both a cause and a consequence of poverty. Poverty increases the conditions which lead to an increased risk of HIV infection, while HIV infection increases vulnerability¹⁰³ to poverty. For example, poverty increases vulnerability to HIV infection due to poor nutrition, lack of access to health care (which would, for example, treat STDs which are risk factors for HIV infection), greater exposure to (sexual and other) violence, the necessity of engaging in transactional sex and the lack of knowledge about preventive methods, and so on. HIV infection, on the other hand, increases poverty because it results in long periods of illness, the death of breadwinners, job loss, lack of access to education, discrimination in the labour market, young children becoming orphans, the increase in single-parent families, and the like.

The HRC's *South African national HIV prevalence, HIV incidence, behaviour and communication survey 2005* bears out the link between poverty and HIV infection rate.¹⁰⁴ The survey distinguishes between HIV prevalence rates for people living in formal and informal settlements, and in rural and urban settings. The HRC's survey shows that people living in informal settlements

100 Cameron 2000 First Jonathan Mann Memorial Lecture: 'The deafening silence of AIDS' XIII International AIDS Conference, Durban, 7-14 July.

101 In many developing countries this is due to a variety of factors, amongst others the lack of links between antenatal or maternity clinics and the so-called "wellness clinics".

102 Barnett and Whiteside 2002:167.

103 'Vulnerability' is used here as indicating those features of an individual or a society which make it more or less likely to become infected with HIV.

104 HSRC 2005:40.

(and therefore belonging to a lower socio-economic group) have a much higher HIV prevalence rate than those in formal housing (urban informal settlements 25.8 per cent prevalence, rural informal settlements 17.8 per cent; compared to 13.9 per cent for both rural and urban formal housing).¹⁰⁵

Anton Van Niekerk comments that poverty:¹⁰⁶

has accompanying side-effects, such as prostitution, (ie the need to sell sex for survival), poor living conditions, education, health and health care, that are major contributing factors to the current spread of HIV/AIDS.

The 'side-effects' of poverty pointed out by Van Niekerk have important implications for the design and conduct of clinical trials in these communities. In poor and desperate communities, where resources are scarce and opportunities even scarcer, where there is limited access to health care, and where unemployment and poverty are the order of the day, research participants may be especially vulnerable to exploitation.¹⁰⁷

South African women are worse hit by the epidemic than men, not only because of the socio-economic factors above, but also because of biological factors.¹⁰⁸ The HRC's survey shows that women between the ages of 15 and 49 have a HIV positive prevalence rate of 20.2 per cent (the antenatal survey of 2004 showed a prevalence rate of 29.5 per cent¹⁰⁹), while men in the same age group have a prevalence rate of 11.7 per cent.¹¹⁰ Women show a prevalence rate almost twice that of men.¹¹¹

105 HSRC 2005:40.

106 Van Niekerk in Van Niekerk and Kopelman 2005:55.

107 Ruth Macklin defines exploitation as occurring 'when wealthy or powerful individuals or agencies take advantage of the poverty, powerlessness, or dependency of others by using the latter to serve their own ends without adequately compensating benefits for the less powerful or disadvantaged individuals or groups' Macklin 2003:475.

108 'Several anatomical and physiological characteristics of women and girls play a role in the transmission and acquisition of HIV. Since the female genital tract has a greater exposed area than the male genital tract, women may be prone to greater per exposure risk of HIV-infection. Coercive or forced sex can lead to microlesions (very small tears in the vagina) that facilitate entry of the virus. Young women, in particular, who have less mature tissue, are more susceptible to infection, as well as more susceptible to coercive sex' (IAVI 2004:2).

109 See fn 110 below.

110 HSRC 2005:38. Incidentally, the HSRC's survey shows a lower overall prevalence rate than other surveys. This could be explained by the fact that other surveys base their statistics on results obtained from women attending antenatal clinics. On the whole, it is African women who attend public health facilities such as antenatal clinics, and they show a much higher prevalence than other race groups which are also included in the HSRC's survey (Africans show an overall HIV prevalence rate of 19.9%, whites 0.5%, coloureds 3.2% and Indians 1.0%) (see HSRC 2005:40). The HSRC's survey also compares the prevalence rate of African females to the 2004 results obtained from the Department of Health's antenatal survey. The results correspond closely — see HSRC 2005:42.

111 There are biological / scientific reasons for this higher prevalence rate, such as women's anatomy making them more susceptible to the virus.

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Adolescent girls and young women are also worse affected than adolescent boys and young men. In the HSRC's survey of youth between the ages of 15 and 24, females show a prevalence rate of 16.9 per cent, males only 4.4 per cent. The overall situation for youth between the ages of 15 and 24 living in informal settlements is dire — they show a prevalence rate of 25.8 per cent.¹¹²

It is not only poverty which increases the conditions which lead to an increased risk of HIV infection; in societies in which women are (considered) unequal to men, unequal power relations between men and women have a similar effect. These relations of unequal power are often the result of women's calamitous socio-economic status:¹¹³

Women's relative powerlessness in heterosex is largely determined by material inequalities that obtain between women and men ... material inequalities that give rise to and are in turn supported by cultural and ideological constructions of gender.

In societies where women are denied access to education they are forced to find menial, low-paying jobs, or they make a living from selling sex to infected partners.¹¹⁴ In such societies women become infected with HIV because they are unable to insist upon safe-sex practices or because of their poor state of nutrition and general health.

Traditional cultural practices, such as dry sex and polygamy¹¹⁵ expose women to HIV infection;¹¹⁶ even monogamous marriage may put women at risk. Virginia Van der Vliet comments as follows on expectations of married African women and their risk of HIV infection:¹¹⁷

... raised in [a] strongly patriarchal society, with a tradition of polygamy, macho ideas of masculinity, and an emphasis on her duty to bear children to ratify bridewealth contracts, [the married woman's] rights to demand fidelity or the use of condoms, or to refuse sex, are, for most women, not negotiable. Economic dependency on her partner weakens her position further.

Other factors exacerbate women's risk of contracting HIV. Anton Van Niekerk remarks:¹¹⁸

112 HSRC 2005:40. The situation is the same in other countries in Southern Africa. Hence the concern to include the youth in HIV vaccine efficacy trials.

113 Alexander and Mbali 'Beyond 'bitches and prostitutes': Folding the materiality of gender and sexuality into rights-based HIV/AIDS interventions' citing Wilson 1997:29 in Viljoen (ed) 2005:51.

114 See eg Karim *et al* 1995:1521.

115 See eg Pieterse 2000:431.

116 Eg dry sex and female genital mutilation. According to Marelise Richter, in her paper on 'Customary law, gender and HIV/AIDS in South Africa' (delivered on 4 August 2003, AIDS Law Project, Centre for Applied Legal Studies), many traditional cultural practices in Africa display an attitude toward women's reproductive ability as a legal object that can be bought and sold. This attitude, in turn, severely limits women's ability to refuse sex or unsafe sex, increasing women's risk of contracting HIV.

117 Van der Vliet 1999:3 cited by Van Niekerk in Van Niekerk and Kopelman 2005:62.

118 Van Niekerk in Van Niekerk and Kopelman 2005:62.

... the grim evidence of a rapid increase in so-called 'sugar daddy' relationships, in which older men seek out younger sexual partners (often mere children) — partly because of their (the men's) perception that young girls might not be infected, while they themselves, of course, often are — and a scary picture of the moral depravity of sectors of South African society emerges. This is an environment very conducive to the flourishing of the AIDS epidemic.

Women who live with HIV/AIDS are stigmatised (sometimes they are even blamed for spreading HIV):¹¹⁹

Moreover, HIV-positive women in these communities [Hammanskraal and Temba] are stigmatised as being prostitutes, or 'loose women', or as having 'invited' HIV infection to claim access to social grants.

Occasionally, women living with HIV/AIDS are killed when they reveal their status, as in the well-publicised case of Gugu Dlamini who was stoned to death by her neighbours.

Stigmatisation leads to discrimination and a violation of equality:¹²⁰

The rights of people living with HIV/AIDS are often violated because of their presumed or known HIV status, causing them to suffer both the burden of the disease and the burden of discrimination. Stigmatisation and discrimination may affect the uptake of [antiretroviral] treatment, and may also affect employment, housing and other rights.

Even worse — women's (and men's) stigmatisation encourages the spread of HIV; because they fear stigmatisation, they do not get tested for HIV, persist in unsafe sexual practices, and the epidemic continues:¹²¹

[t]his, in turn, contributes to the vulnerability of others to infection, since HIV-related stigma and discrimination discourages (*sic*) individuals infected with and affected by HIV from contacting health and social services.

It is important to emphasise the point made in the quote above: not only do poverty, women's inequality and stigmatisation create greater vulnerability to HIV infection, but they also compound a vicious circle whereby people who are infected with HIV are further stigmatised and discriminated against, creating greater poverty and inequality, and, in turn, causing the exposure of others to the disease. This self-perpetuating circle epitomises the relationship between poverty, gender inequality and stigmatisation and HIV infection. Poverty, gender inequality and stigmatisation increase the risk for HIV infection, and the impact of HIV infection deepens poverty, stigmatisation and gender inequality; putting others at risk of infection, and resulting in further impoverishment.

119 Alexander and Mbali in Viljoen (ed) 2005:51.

120 Zuberi "If you (be)come HIV positive, you will lose your human rights" — HIV/AIDS stigma and human rights: A localised investigation of Hammanskraal communities' in Viljoen (ed) 2005:13.

121 Viljoen 2005:13.

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The MRC's vaccine trial guidelines explain this complicated interrelationship between poverty, women's inequality and stigmatisation, and its implications for HIV vaccine trials:¹²²

HIV/AIDS is a condition that is both highly feared and stigmatised, largely because it is associated with blood, sex, and illegal activities such as commercial sex. As these issues are difficult to address openly, people affected by HIV/AIDS in South Africa experience stigma, discrimination, and even violence. Vulnerability to HIV infection is greater *where people are marginalised* due to their *social or legal status*. These factors *increase the risk of social and psychological harm* for people participating in HIV vaccine trials. Additional efforts must be made to minimise these risks, and to ensure that risks are justified by the benefits. *Meaningful community participation and authentic informed consent are critical safeguards.*

In order to demonstrate the efficacy of the candidate HIV vaccine, participants in HIV vaccine efficacy trials logically need to be at high risk for HIV infection and, as indicated above, vulnerability to HIV infection is "greater where people are marginalised due to their social or legal status". Communities at high risk for HIV infection in South Africa, as elsewhere, are those that are poor, and where there are inequality and stigmatisation. It is in these communities where HIV vaccine trials are likely to take place.

The socio-economic status of a community has important implications for the design and conduct of clinical trials, and for obtaining informed consent from participants.¹²³ Zion remarks:¹²⁴

... in an environment where the majority can neither read or write and is wallowing in poverty and sickness, hunger and homelessness, and where the educated, the powerful, the rich, or the expatriate is a semi-god, how can you talk of informed consent?

In the light of the conditions prevailing at the point of potential South African Phase III preventive HIV vaccine trial sites, obtaining informed consent from participants in these trials may present difficulties.¹²⁵ It is therefore necessary to examine the extent of the protection offered vaccine trial participants in section 12(2)(c) of the Constitution.

3. Informed consent as a human right entrenched in section 12(2)(c) of the South African Constitution

The Constitution of the Republic of South Africa 1996 is the supreme law¹²⁶ of the Republic. The human rights entrenched in Chapter 2 bind the legislature, the judiciary, the executive and all organs of state and apply to all law (statutes,

122 MRC 2002:Book V, 'Context' 4. My emphasis.

123 These implications are discussed below.

124 Zion quoted by Moodley in Van Niekerk and Kopelman 2005:174.

125 For a discussion of some of these difficulties, see Nienaber 2007:490-508.

126 Constitution of the Republic of South Africa 1996: section 2.

common law, and customary law).¹²⁷ Any law or conduct that is in conflict with the Constitution may be struck down as unconstitutional and void.¹²⁸

A statutory body (such as a university or the Medical Research Council), or a private pharmaceutical company doing HIV vaccine efficacy trials, is bound to respect the research participant's constitutional right to informed consent. In terms of section 8(2), "[a] provision in the bill of rights binds a natural or a juristic person if, and to the extent that, it is applicable, taking into account the nature of the right and the nature of the any duty imposed by the right". The duty imposed by section 12(2)(c) — to respect an individual's right not to be subjected to experimentation without informed consent — is not an onerous one,¹²⁹ and therefore binds a statutory body, such as a university, as well as a private pharmaceutical company.

Various rights guaranteed in the Constitution find application to the position of participants in HIV vaccine research, namely, the right to life;¹³⁰ the right to human dignity;¹³¹ the right to equality;¹³² the right to privacy;¹³³ the right of access to health care;¹³⁴ and the focus of this discussion, the right to bodily and psychological integrity.¹³⁵ In *Ex Parte Minister of Safety and Security and Others: In Re S v Walters and Another*,¹³⁶ Judge Kriegler remarked on the interrelationship between section 12 and other rights, as well as the importance of these rights:¹³⁷

What looms large in both the threshold and the limitations phases of the exercise in the present case is that the right to life, to human dignity and to bodily integrity are individually essential and collectively foundational to the value system prescribed by the Constitution. Compromise them and the society to which we aspire becomes illusionary. It therefore follows that any significant limitation of any of these rights would for its justification demand a very compelling countervailing public interest.

At the risk of defining the problem too narrowly, the article limits the investigation to the protection of informed consent in section 12(2)(c), which reads: "[e]veryone has the right to bodily and psychological integrity, which includes the right ... not to be subjected to medical or scientific experiments without their informed consent".

127 Section 8(1) of the Constitution.

128 Section 2 of the Constitution; *Executive Council of the Western Cape Legislature v President of the Republic of South Africa* 1995 (4) SA 877 (CC) para 62; *Fose v Minister of Safety and Security* 1997 (3) SA 786 para 87.

129 Such as would probably be duties imposed by socio-economic rights such as the right to health care (section 27).

130 Section 11 of the Constitution.

131 Section 10 of the Constitution.

132 Section 9 of the Constitution.

133 Section 14 of the Constitution.

134 Section 27(1)(a) of the Constitution.

135 Section 12(2) of the Constitution.

136 *Ex Parte Minister of Safety and Security and Others: In Re S v Walters and Another* 2002 (4) SA 613 (CC).

137 As above, para 28.

This subsection is part of the wider guarantee in section 12 to freedom and security of the person. Section 12 consists of two distinct parts: subsection 1, which deals with freedom and security of the person; and subsection 2, which deals with the right to bodily and psychological integrity, of which subsection 12(2)(c) is part. Van Wyk remarks that section 12 “deals with freedom from *direct* physical abuse in three of its most fundamental senses (freedom from violence, torture, cruel and degrading treatment and medical and scientific experimentation)”.¹³⁸

The right to bodily and psychological integrity in section 12 is stated in general terms — “[e]veryone has the right to bodily and psychological integrity”. After this general statement, the subsection mentions three specific instances of bodily and psychological integrity, namely, the right to make decisions concerning reproduction;¹³⁹ the right to security in and control over their body;¹⁴⁰ and the right not to be subjected to medical or scientific experiments without their informed consent.¹⁴¹ The three specific instances of the general right to bodily and physical integrity are introduced by the phrase “... which includes the right ...”. The word “includes” indicates that these are only some of the many possible manifestations of the right to physical and psychological integrity.

The inclusion of subsection 12(2)(b) — “the right to security in and control over their body” is puzzling: at first glance it seems to be a mere restatement of the more general guarantee of “bodily and psychological integrity”. Woolman and Bishop assert that section 12(2)(b) tests “our ability to give distinct meaning to ‘bodily and psychological integrity’, on the one hand, and ‘security in and control over the body’, on the other ... we must interpret ‘bodily and psychological integrity’ to mean something over and above ‘security in and control over’ the body”.¹⁴² According to Woolman and Bishop, section 12(2)(b):¹⁴³

creates a sphere of individual inviolability. Section 12(2)(b) tells us that this inviolability has two components. ‘Security in’ and ‘control over’ one’s body are not synonymous. The former denotes the protection of bodily integrity against physical invasions by the state and others. The latter guarantees the freedom to exercise autonomy or the right to self-determination with respect to the use of one’s body.

It is precisely the right to autonomy, implicit in the second component of the section 12(2)(b) right, that underpins the right to make informed decisions about whether to participate in research — the right to self-determination to decide whether to participate in research. Research without informed consent would amount to a violation of the first component of the right as it amounts to an invasion of one’s body.

138 Van Wyk 2001:18. Original emphasis.

139 Section 12(2)(a).

140 Section 12(2)(b).

141 Section 12(2)(c).

142 Woolman and Bishop in Woolman *et al* (eds) 2005:40-57–40-58.

143 Woolman and Bishop in Woolman *et al* (eds) 2005:40-63.

Are the “right to bodily integrity” in 12(2), as well as the right to “security in and control over their body” not broad enough to embrace protection against research without informed consent? Why does section 12 make explicit mention of “the right not to be subjected to medical or scientific experiments without their informed consent”?

Various answers to these questions are suggested: the right to informed consent is mentioned explicitly in the International Covenant on Civil and Political Rights; the inclusion of the right might be a reaction to abuses during the previous constitutional dispensation when research subjects were perhaps subjected to medical experimentation without informed consent; and the inclusion of informed consent as a constitutional imperative highlights the importance ascribed to autonomy — section 12(2)(c) “alerts us to the threats to personal integrity that flow from everyday medical research and treatment”.¹⁴⁴

The use of ‘everyone’ in the section indicates that the rights conferred in section 12 are not limited to South African citizens. Section 12 is not a political right (which normally indicates that the right applies to citizens only); the right applies to citizens and non-citizens. Everyone in South Africa taking part in HIV vaccine efficacy trials may rely on section 12(2)(c) to protect their interests.¹⁴⁵

Van Wyk is of the opinion that “experimentation” as used in section 12(2)(c) probably means medical or scientific “research”.¹⁴⁶ The view is correct, given the fact that the two terms are used interchangeably in various international ethical documents and the *National Health Act*.¹⁴⁷ After an exhaustive analysis of the matter, Van Wyk remarks regarding the interpretation to be given to the term “experiment” in section 12(2)(c):¹⁴⁸

The question now is which interpretation can be given to the term ‘experiment’. The first option equates ‘experiment’ with research, whether it is of a therapeutic or non-therapeutic nature. This seems to be the straightforward, literal meaning, which is also compatible with most of the sources dealing with research ethics quoted above. It is also in keeping with a purposive, generous interpretation of the right not to be subjected to research without one’s own consent, in that it gives effect to the right to personal dignity, integrity and autonomy in its widest sense. When section 12(2)(c) is read in context with the whole of section 12 — which deals with the freedom and security of the person — the conclusion is the same.

Another important aspect of section 12(2)(c) is the mention of medical or *scientific* experiments. The drafting history of the subsection shows that the

144 Woolman and Bishop in Woolman *et al* (eds) 2005:40-69.

145 This statement oversimplifies the situation, and does not account for the position of temporary and permanent residents, nor does it account for the position of persons who are illegally in the country. In this regard, see Klaaren 1998:286.

146 Van Wyk 2004:8.

147 See eg the Nuremberg Code, which refers to ‘experimentation’; the CIOMS Guidelines which refer to ‘research’ and the Declaration of Helsinki, which refers to both ‘experimentation’ and ‘research’. Also, the *National Health Act* 61/2003 refers to ‘experimentation’ and ‘research’ as alternatives for the same concept.

148 Van Wyk 2001:18.

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words *or scientific*, are a later addition to the drafting of the subsection — added to the March 1995 draft of the Bill of Rights.¹⁴⁹ The inclusion of the word “or” indicates that “scientific” is something different from “medical”. “Scientific” is certainly a term wider in meaning than medical; most medical experimentation may be termed “scientific”, not all scientific experiments are “medical”. Not only experimentation in the medical sciences, but also other “scientific” experiments which are conducted using human subjects fall under the ambit of section 12(2)(c). In this regard, is experimentation in, for example, the human sciences, included in the term “scientific” as human subjects are often used in such experiments? It is submitted that the answer to this question is positive: all experimentation on human subjects, whether in the human or natural sciences, requires the informed consent of research subjects.

In addition, section 12(2)(c) makes no distinction between therapeutic and non-therapeutic experimentation, unlike the *National Health Act*.¹⁵⁰ All experimentation without the participant’s informed consent is prohibited, regardless of the category to which it belongs. It is unlikely that the distinction between “medical *or scientific* experiments” is meant to separate therapeutic (medical) from non-therapeutic (scientific) research.

The use of the word “their” in section 12(2)(c) has elicited comment from scholars. Van Oosten remarks: “The use of the word “their” in section 12(2)(c) makes it patently clear that the only person who is capable of giving consent to medical research is the research participant and that surrogate consent to medical research is out of the question”.¹⁵¹ Van Oosten thus suggests that no research may be allowed on persons incapable of giving their own consent. Van Oosten argues that surrogate consent to medical research on incompetent minors and mentally ill persons is impossible — an overly strict interpretation of the word “their”. Van Wyk’s view is preferable to that of Van Oosten. She argues convincingly that:¹⁵²

[Van Oosten’s strict interpretation] would preclude research in South Africa on legally incompetent people, such as young children, who are not capable of providing voluntary informed consent. This would also preclude research where proxy consent from their parents or care-givers is obtained. This would render South Africa out of step with the rest of the world in this respect, and would undeniably hinder medical progress.

Van Wyk would allow “therapeutic” research on other than competent individuals, as long as the necessary surrogate consent has been obtained.¹⁵³ It is submitted that non-therapeutic or “scientific” research on incompetent people, which carries more than minimal risk, is not allowed under the South African Constitution.¹⁵⁴ HIV vaccine efficacy trials, as they carry significantly

149 See Woolman and Bishop in Woolman *et al* (eds) 2005:40-5, fn 3.

150 See Nienaber 2008:forthcoming.

151 Van Oosten 1989:9.

152 Van Wyk 2005:38.

153 See Van Wyk 2004:8.

154 Article 7 of ICCPR, however, allows for such research in certain circumstances, if certain requirements are met.

more than minimal risk, thus, cannot be carried out on incompetent minors or mentally ill persons.

Few reported cases on informed consent as embodied in section 12(2)(c) subsequent to the enactment of the 1996 Constitution have reached the South African courts. The 2004 Cape High Court case of *Oldwage v Louwrens*,¹⁵⁵ and its 2006 reversal on appeal, *Louwrens v Oldwage*,¹⁵⁶ therefore, merit attention.

In *Oldwage v Louwrens* the Cape High Court had to decide whether the medical practitioner misrepresented a particular procedure to relieve pain. The Cape High Court affirmed that informed consent should be based on a “substantial knowledge of *all the material risks*” of the procedure. It held that the principles laid down by the Court in *Casstell v De Greef*¹⁵⁷ set the standard for determining whether a patient gave informed consent to a procedure.

On appeal, the Supreme Court of Appeal quoted and approved of the requirements for informed consent to operate as a defence laid down by Judge Ackermann in *Castell v De Greef*. They are, *inter alia*:¹⁵⁸

- (a) the consenting party “must have had knowledge and been aware of the nature and extent of the harm or risk”;
- (b) the consenting party “must have appreciated and understood the nature and extent of the harm or risk”;
- (c) the consenting party “must have consented to the harm or assumed the risk”;
- (d) the consent “must be comprehensive, that is extend to the entire transaction, inclusive of all its consequences”.

Overtuning the Cape High Court’s judgment on the facts, the Supreme Court of Appeal held that it was not expected of a surgeon to warn a patient of the likelihood of a complication in a procedure if there was a mere 2 per cent chance of this risk materialising; that is, the Supreme Court of Appeal affirmed the requirement that informed consent should be based on knowledge of the “material risks” of a procedure.

Carstens and Pearmain argue that, in view of previous legal opinion and case law, the judgment of the Supreme Court of Appeal in *Louwrens v Oldwage* is “ambivalent, confusing and contentious”.¹⁵⁹ They criticise the Court on a number

155 *Oldwage v Louwrens* 2004 (1) SA 532 (C). However, this is not the only case on section 12 to reach the courts. For example, in *Minister of Safety and Security and Another v Xaba* (2002 (2) SA 703 (D)), the court refused to grant an order that would allow a bullet to be removed from a prisoner’s leg without his consent on the basis that the prisoner’s section 12 rights would be infringed by such an operation. Also relevant to the protection offered by section 12 are *Christian Lawyers Association of South Africa v Minister of Health* 1998 (4) SA 1113 (T), 1998 (11) BCLR 1434 (T).

156 *Louwrens v Oldwage* 2006 (2) SA 161 (SCA).

157 *Castell v De Greef* 1994 (4) SA 408 (C).

158 *Louwrens v Oldwage* 2006 (2) SA 161 (SCA) para 22B-C.

159 Carstens and Pearmain 2007:683.

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of grounds, but most relevant to the current discussion, for simultaneously applying *Castell v De Greef* and *Richter v Estate Hammann*, and thereby invoking the discarded standard of the reasonable doctor in the context of informed consent.¹⁶⁰

Moreover, Carstens and Pearmain criticise the Supreme Court of Appeal for following a one-dimensional approach which ignores the impact of the Constitution on the existing law on informed consent. They observe that:¹⁶¹

in addition the court follows, in context of the issue of informed consent, a one-dimensional approach, by only referring to some common law principles relating to informed consent. There is a total absence of the multi-layered approach which is now indicated in terms of the transcendental nature of medical law in the context of the constitutional paradigm — ie in addition to the common law, the applicable provisions of the Constitution (particularly section 12(2)(b) dealing with bodily integrity) and applicable legislation governing informed consent (sections 6 and 7 of the National Health Act). In the absence of an assessment of these considerations impacting on informed consent, one has to state, that the judgment, in this regard is with respect, not well-considered (as opposite to the principled judgment by Yekiso J in the court *a quo*).

It is submitted that Carstens' and Pearmain's criticism of the case is well-founded. *Louwrens v Oldwage* is the first case to reach the Supreme Court of Appeal after the enactment of the 1996 Constitution; however, the Court missed an ideal opportunity to provide a well-nuanced and principled approach to informed consent in South African law in the light of the Constitution, and to clear up uncertainty surrounding the question of whether a lack of informed consent constitutes assault or negligence.¹⁶²

One more case needs mention. In *McDonald v Wroe*,¹⁶³ in dealing with a dentist's failure to warn his patient about the risk of permanent nerve damage during the extraction of her wisdom teeth, the Cape Provincial Division found that the plaintiff's right to bodily integrity entrenched in section 12(2) of the Constitution was infringed. The Court remarks:¹⁶⁴

In obtaining plaintiff's consent to the procedure, defendant failed to fully inform her of the nature and extent of the risk of permanent nerve damage, with the result that plaintiff consented thereto without appreciating the risk of permanent nerve damage. Defendant's omission is accordingly linked to the harm suffered by plaintiff. To this I should add that plaintiff's right to bodily integrity is entrenched in section 12(2) of our Constitution of the Republic of South Africa, 1996, which right the defendant has violated by subjecting her to surgery without obtaining her informed consent.

160 Carstens and Pearmain 2007:685.

161 Carstens and Pearmain 2007:686.

162 In this regard, see Nienaber 2008:forthcoming.

163 *McDonald v Wroe* [2006] 3 All SA Law Reports 565; also discussed in Carstens and Pearmain 2007:634.

164 *McDonald v Wroe* 575, para 39.

4. Conclusion

It is extremely urgent that preventive HIV vaccine efficacy trials be undertaken. The second section of the article outlines the socio-economic context of HIV vaccine efficacy trials in South Africa, showing how aspects of the South African socio-economic context, such as dire poverty, women's inequality and stigmatisation, not only increase certain communities' vulnerability to HIV infection, thereby accelerating the spread of the disease, but also increase those communities' vulnerability to exploitation and abuse during HIV vaccine efficacy trials.

It is difficult to ensure the informed consent of HIV vaccine trial participants in South Africa. Moodley remarks that the concept of informed consent in the South African context is "riddled with intricacies"; and that,¹⁶⁵

[i]n the aftermath of the apartheid era in South Africa, many people who are completely competent still relinquish their decision-making rights to authority figures, be they doctors, researchers or both. This is accentuated when researchers and study participants belong to different racial groups and where asymmetrical power relationships, based on the previous apartheid system, exist. Enormous efforts are required on the part of the medical profession and researchers to create the level of understanding necessary to meet the criteria of competence. Coupled with this is the need for empowerment of many patients, who, as a result of decades of oppression, have never learned how to exercise their decision-making rights.

In these circumstances it is important to establish the extent of the protection offered by section 12(2)(c) of the Constitution, which is done in the third section of the article. It is remarked that the right to autonomy is implicit in section 12(2), and that it underpins the right to make informed decisions about whether to participate in clinical research. Research without informed consent amounts to a violation of the research participant's right to bodily integrity as it amounts to an invasion of the participant's body.

It is argued that the use of 'everyone' in section 12 indicates that the rights conferred in section 12 are not limited to South African citizens — everyone in South Africa taking part in HIV vaccine efficacy trials may rely on section 12(2)(c) to protect their interests. As well, not only experimentation in the medical sciences, but also other "scientific" experiments which are conducted using human subjects fall under the ambit of section 12(2)(c).

Section 12(2)(c) makes no distinction between therapeutic and non-therapeutic experimentation, unlike the *National Health Act*. Therefore, all experimentation without the participant's informed consent is prohibited, regardless of the category to which it belongs. Van Wyk's view that "therapeutic" research on incompetent persons is allowed by section 12(2)(c), as long as the necessary surrogate consent has been obtained, is supported. However, non-therapeutic research on incompetent people, which carries more than minimal risk, is not allowed under section 12(2)(c) of the South African Constitution. It is proposed

165 Moodley 2002:204.

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that HIV vaccine efficacy trials, which carry significantly more than minimal risk, cannot be carried out on incompetent minors or mentally ill persons. HIV vaccine efficacy trials on competent people, on the other hand, are not precluded by section 12(2)(c).

Case law subsequent to the enactment of section 12(2) is discussed in the article in order to discover the influence of the constitutional guarantee on informed consent law. It is concluded that *Louwrens v Oldwage* — the first case to reach the Supreme Court of Appeal after the enactment of the 1996 Constitution — overlooks the impact of the Constitution on informed consent law in South Africa. The Supreme Court of Appeal follows a rather one-dimensional approach, referring to common law principles relating to informed consent, and ignoring section 12(2). It is submitted that Carstens' and Pearmain's criticism of the case is well-founded: the Court missed an ideal opportunity to provide a well-nuanced and principled approach to informed consent in South African law in the light of the Constitution. It is to be hoped that this omission will be rectified in future jurisprudence of the Supreme Court of Appeal.

In contrast to *Louwrens v Oldwage*, in *McDonald v Wroe* the Cape High Court takes cognisance of the constitutional guarantee contained in section 12(2), interpreting the common law principles on informed consent in the light of the plaintiff's right to bodily integrity as entrenched in section 12(2) of the Constitution. The Court holds that the defendant has violated this right by subjecting the plaintiff to surgery without obtaining her informed consent.

The South African constitutional system recognises constitutional supremacy. This means that section 12(2)(c) offers supreme protection in terms of informed consent in South Africa — it is a vital constitutional imperative. Preventive HIV vaccine research protocols which violate participants' section 12(2)(c) right not to be subjected to medical experimentation without their informed consent are prohibited. Whether such a violation occurs in a specific situation is a factual question to be determined by a court.¹⁶⁶

The constitutional guarantee contained in section 12(2)(c), therefore, is an important buttress against communities' exploitation during HIV vaccine efficacy trials. Its importance lies in its power to transform oppressive conditions such as poverty, women's inequality and stigmatisation by introducing processes that endorse vaccine trial participants' autonomy and physical integrity as fundamental rights.

166 A court will have to determine whether the conduct in question constitutes 'medical experimentation', and whether informed consent was given.

Bibliography

- ABDOOL KARIM SS
2002. Conducting HIV vaccine trials in South Africa. *CME* 20(9):588.
- AINSWORTH M, FRANSEN L AND OVER M (eds)
2000. *Confronting AIDS: Evidence from the developing world*. Brussels: European Commission.
- AVAC
2006. *AIDS vaccines report: The next frontiers*. New York: AVAC.
- BARNETT T AND WHITESIDE A
2002. *AIDS in the twenty-first century: Disease and globalization*. Houndmills: Palgrave.
- BARRY C AND RAWARTH K
2002. Access to medicines and the rhetoric of responsibility. *Ethics and International Affairs* 16:57-70.
- BENATAR SR
2005. The HIV/AIDS pandemic: A sign of instability in a complex global system. In Van Niekerk and Kopelman (eds) 2005: 71-83.
- CAMERON E
2000. First Jonathan Mann Memorial Lecture: The deafening silence of AIDS. XIII International AIDS Conference, Durban, 7-14 July 2000.
- CARSTENS P AND PEARMAIN D
2007. *Foundational principles of South African medical law*. Durban: Lexis-Nexis.
- CELENTANO DD, BEYRER C, NATPRATAN C, EIUMTRAKUL S, SUSSMAN L, RENZULLO PO, KHAMBOONRUANG C AND NELSON KE
1995. Willingness to participate in AIDS vaccine trials among high-risk populations in northern Thailand. *AIDS* 9:1079-1083.
- COLLETTI AS, HEAGERTY PJ, SHEON A, GROSS M, KOBLIN B, METZGER D AND SEAGE G
2003. Randomized, controlled evaluation of a prototype informed consent process for HIV vaccine efficacy trials. *Journal of Acquired Immune Deficiency Syndromes* 32:161-169.
- FARHAM B
2006. The trials of testing. Unpublished paper, on file with author.
- FOSTER C
2001. *The ethics of medical research on humans*. Cambridge: Cambridge University Press.
- FRANCIS DP, HEYWARD WL, POPOVIC V, OROZCO-CRONIN P, ORELIND K, GEE C, HIRSCH A, IPPOLITO T, LUCK A, LONGHI M, GULATI V, WINSLOW N, GURWITH M, SINANGIL F AND BERMAN PW
2003. Candidate HIV/AIDS vaccines: Lessons learned from the world's first phase III efficacy trials (editorial review). *The Lancet* 17:147.
- GRAHAM BS AND WRIGHT PF
2003. Candidate AIDS vaccines. *The New England Journal of Medicine* 33: 1331-1339.
- HSRC
2005. *South African national HIV prevalence, HIV incidence, behaviour and communication survey*. Cape Town: HSRC Press.
- IAVI
2004. *Gender in HIV vaccine trials: Addressing challenges in developing countries*. New York: IAVI.
- JANSE VAN RENSBURG E
2002. Vaccine design and making vaccines for South Africa. *CME* 20:577-580.
- JASPAN HB, BEKKER L, GRAY GE, ROBINSON AKL AND COOVADIA HM
2005. Scientific justification for the participation of children and adolescents in HIV-1 vaccine trials in South Africa. *South African Medical Journal* 95:685-687.

Nienaber/Informed consent to participation in preventive HIV vaccine efficacy trials in the light of section 12(2)(c) of the South African Constitution

- KARIM QA, SARIM S, SOLDAN K AND ZONDI M
1995. Reducing the risk of HIV transmission among South African sex workers: Gender and socio-economic barriers. *American Journal of Public Health* 85:1521-1525.
- KEAY K, TACKET CO, MURPHY JR AND HANDWERGER BS
1992. Anti-CD4 anti-idiotypic antibodies in volunteers immunized with rgp160 of HIV-1 or infected with HIV-1. *AIDS Research on Human Retroviruses* 8:1091-1098.
- KLAAREN J
1998. Non-citizens and equality. *South African Journal on Human Rights* 14: 286-297.
- KLEIN E AND HO RJY
2000. Challenges in the development of an effective HIV vaccine: Current approaches and future directions. *Clinical Therapeutics* 22:295-314.
- LEVINE RJ
1986. *Ethics and regulation of clinical research*. 2nd ed. New Haven: Yale University Press.
- LOCHER CP, GRANT RM, COLLISSON EA, REYES-ETERAN G, ELBEIK T, KAHN JO AND LEVY JA
1999. Antibody and cellular immune responses in breakthrough infection subjects after HIV type 1 glycoprotein 120 vaccination. *AIDS Research* 71:1685-1759.
- MACKETT M AND WILLIAMSON JD
1995. *Human vaccines and vaccination*. Oxford: BIOS Scientific Publishers.
- MACKLIN R
2003. Bioethics, vulnerability, and protection. *Bioethics* 17:472-486.
- MCCARTHY M
1997. AIDS doctors push for live-virus vaccine trials. *The Lancet* 350:1083.
- MOODLEY K
2005. HIV vaccine trial participation in South Africa — An ethical assessment. In Van Niekerk and Kopelman (eds) 2005: 160-178.
- MRC
2002. *Guidelines on ethics for medical research*. 4th ed. Pretoria: MRC Press.
- NIAID NIH
2003. Challenges in designing vaccines. Available at <<http://www.naid.nih.gov/factsheets/challenges/challvacc.htm>>.
- NICKLIN J, PAGET T, GRAEME-COOK K AND KILLINGTON RA
1999. *Notes in microbiology*. Oxford: BIOS Scientific publishers.
- NIENABER A G
2007. Ethics and human rights in HIV-related clinical trials in Africa with specific reference to informed consent in preventative HIV vaccine efficacy trials in South Africa. Unpublished LLD thesis, University of Pretoria.
2008. The researcher's liability for HIV-related clinical research without the participant's informed consent: South Africa's common law, case law and legislation. *THRHR* (forthcoming).
- PIETERSE M
2000. Beyond the reach of law? HIV, African culture and customary law. *Journal of South African Law* 3:431-441.
- RESNIK DB
2001. Developing drugs for the developing world: An economic, legal, moral, and political dilemma. *Developing World Bioethics* 1:11-32.
- RICK NG
2004. *Drugs: From discovery to approval*. Hoboken, NJ: John Wiley & Sons.
- RUMENAPF EG, STRAUSS EG AND STRAUSS JH
1995. Aura virus is a New World representative of Sindbis-like viruses. *Virology* 208:621-633.

RUFF TA

2002. Vaccine research and development. *Internal Medicine Journal* 32: 127-128.

SAAVI

2003. Medicines Control Council approves first HIV vaccine trial in South Africa. SAAVI press release, 18 June 2003.

2006. Annual Report 2004/2005.

SCHOUB BD

1994. *AIDS and HIV in perspective*. Cambridge: Cambridge University Press.

2002. Vaccination as an intervention against viral diseases: Will this work for HIV? *CME* 20:561.

SLACK C, LINDEGGER G, VERDAS E, RICHTER L, STRODE A AND WASSENAAR D
2000. Ethical issues in HIV vaccine trials in South Africa. *South African Journal of Science* 96:291-295.

SLACK C, MILFORD C, STRODE A AND GRANT C
2005. Implications of the ethical-legal framework for adolescent HIV vaccine trials — report of a consultative forum. *South African Medical Journal* 95:682-684.

SACK C AND KRUGER M
2005. The South African Medical Research Council's Guidelines on Ethics for Medical Research — implications for HIV preventative vaccine trials with children. *South African Medical Journal* 95:269-271.

STRODE A, SLACK C, GRANT K AND MUSHARIWA M
2005. Ethical and legal challenges in enrolling adolescents in medical research in South Africa: Implications for clinical trials. *South African Journal of Sciences* 101:224-228.

TANGWA GB
2001. Moral agency, moral worth and the question of double standards in medical research in developing countries. *Developing World Bioethics* 1:156-162.

UNAIDS

2000. *Ethical considerations in HIV preventative vaccine research*. Geneva: WHO/UNAIDS.

2006. *AIDS epidemic update*. Geneva: WHO/UNAIDS.

VAN DER VLIET V

1999. V The ecology of South Africa's AIDS epidemic. *Pulse Track* July:1.

VAN HARMELEN J AND WILLIAMSON C
2000. HIV complexity: Challenges in vaccine development. *CME* 20:568-573.

VAN NIEKERK AA AND KOPELMAN LM (eds)
2005. *Ethics and AIDS in Africa: The challenge to our thinking*. Claremont: David Philip Publishers.

VAN OOSTEN FW
1989. The doctrine of informed consent in medical law. Unpublished LLD thesis, University of South Africa.

VAN STADEN CW
2007. Can involuntary admitted patients give informed consent to participation in research? *South African Journal of Psychiatry* 13:10-12.

VAN WYK C
2001. Guidelines on medical research ethics, medical "experimentation" and the Constitution. *THRHR* 64:3-22.

2005. HIV preventative vaccine research on children: Is this possible in terms of South African law and research guidelines? *THRHR* 68:35-50.

VELJKOVIC V, MULLER S AND KOHLER H
2003. AIDS-VAX results: An important open question. *Vaccine* 21: 3528-3529.

VELJKOVIC V, PRLJIC J AND VELJKOVIC T
2004. Safety and ethical considerations of AIDS vaccine. *International Review of Immunology* 23:465-486.

VILJOEN F (ed)
2005. *Righting stigma: Exploring a rights-based approach to addressing stigma*. Pretoria: AIDS and Human Rights Research Unit, UP.

Nienaber/Informed consent to participation in preventive HIV vaccine efficacy trials in the light of section 12(2)(c) of the South African Constitution

- WEAVER SC, HAGENBAUCH A, BELLEW LA, NETESOV SV, VOLCHKOV VE, CHANG GJJ, CLARKE DK, GOUSSET L, SCOTT TW, TRENT DW AND HOLLAND JJ
1993. A comparison of the nucleotide sequences of eastern and western equine encephalomyelitis viruses with those of other alphaviruses and related RNA viruses. *Virology* 197: 375-390.
- WEIDLE PJ, MASTRO TD, ALISON DG, NKENGASONG J AND MACHARA D
2002. HIV/AIDS treatment and HIV vaccine trials for Africa. *The Lancet* 359: 2261-2267.
- WHO
1998. *The world health report — 1998*. Geneva: WHO.
- WILLIAMSON A-L
2002. The development of HIV-1 subtype C vaccines for Southern Africa. *Life* 53:207-208.
- WOOLMAN S, ROUX T AND BISHOP M (eds)
2005. *Constitutional law of South Africa*. 2nd ed. Kenwyn: Juta & Co.