HIV prevention responsibilities in HIV vaccine trials: Complexities facing South African researchers

Zaynab Essack, Catherine Slack, Jennifer Koen, Glenda Gray

Researchers should protect the welfare of research participants through providing methods to reduce their risk of acquiring HIV. This is especially important given that late-phase HIV vaccine trials enrol HIV-uninfected trial volunteers from high-risk populations.

Current ethical guidelines may be difficult for stakeholders to implement, and we know very little about what prevention services researchers are currently providing to participants or their successes, best practices and challenges. We recommend that current normative guidance be systematically reviewed and actual practice at vaccine sites be documented.

Adding new tools to the current package of prevention services will involve complex decision making with few set standards, and regulatory and scientific challenges. We recommend that stakeholders (including regulators) convene to consider standards of evidence for new tools, and that decision-making processes be explicitly documented and researched. A further critical ethical task is exploring the threshold at which adding new tools will compromise the validity of trial results.

S Afr Med J 2010; 100: 45-48.

Background, aims and methodology

Preventing new HIV infections is critical. However, less than one in five people has access to proven prevention methods,[1] and 'for every person placed on antiretroviral treatment in 2006, another six people became newly infected with HIV'.[2] Efforts to utilise existing prevention strategies better, and to identify new ones, are therefore imperative.[3] Apart from male circumcision, results of several prevention trials have been disappointing, including the use of acyclovir to reduce HIV transmission by suppressing herpes simplex virus type 2 (HSV2). Although not statistically significant, the PRO 2000 microbicide gel results are promising and more results, such as pre-exposure prophylaxis (PrEP), are expected in the next few years.

As South Africa is the epicentre of the HIV epidemic, several clinical trials have been conducted or are ongoing, including HIV vaccines, microbicides, PrEP, herpes suppression, cervical barriers, male circumcision and behavioural interventions.[4] Several preventive HIV vaccine trials (HVTs) have been conducted in South Africa since 2003 (5 phase I trials, 2 phase II trials, and 1 phase IIb trial). Three of these are ongoing, namely HVTN 204, a phase II trial assessing the safety and immunogenicity of a multiclade HIV-1 DNA vaccine boosted by a multiclade HIV-1 Ad5 vaccine in HIV-uninfected adults, in which 240 of the 480 participants are South Africans who have received all their vaccinations and are being followed up for long-term safety and immunogenicity; the SAAVI 102/HVTN 073 trial, investigating the multigene sub-type C SAAVI DNA-C2 and MVA-C vaccine, a phase I trial currently enrolling participants, of whom 36 out of the 48 will be enrolled in South Africa; and the HVTN 503 phase IIB trial, in which 801 participants are being followed up after further enrolments and vaccinations were halted.

We outline the complexities facing researchers with regard to their prevention responsibilities in HVTs and make recommendations for future work. A literature search of electronic databases and key websites was conducted for publications relating to the standard of prevention. A conceptual analysis of this literature and key ethical guidelines pertaining to HVTs was undertaken.

Responsibility to provide proven/established effective methods

Current *international* ethical guidelines[2] assert that 'researchers, research staff and trial sponsors should ensure that … access to all *state of the art* HIV risk reduction methods are provided to participants' (Guidance Point (GP) 13, p. 45), they should 'receive all *established effective* HIV risk reduction measures' (GP 15, p. 51) and participants are 'entitled' to proven prevention methods. *South African* guidance articulates that participants should receive *access to preventive methods*,[5] later described as '*optimal*' (p. 28) (our emphasis throughout the above paragraph).

HIV/AIDS Vaccines Ethics Group (HAVEG), School of Psychology, University of KwaZulu-Natal, Pietermaritzburg
Zaynab Essack, MSocSci (Research Psychology)
Catherine Slack, MA (Clinical Psychology)
Jennifer Koen, BA (Hons)

HIV/AIDS Vaccine Division, Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg
Glenda Gray, MB BCh, FCPaed (SA)

Corresponding author: *Z Essack (essack@ukzn.ac.za)*

UNAIDS-WHO[2] outlines that all trial participants should receive access to risk reduction counselling on safer sex, education concerning general health, the benefits of post-exposure prophylaxis (PEP) and strategies to reduce domestic violence; male and female condoms; sexually transmitted infection (STI) treatment; sterile injecting equipment and medical substitution therapies such as methadone maintenance; PEP; and reproductive health care services including access to family planning, appropriate contraception, pregnancy and childbirth services. The South African guidance concurs on access to counselling, condoms, STI treatment and counselling on the benefits of PEP (cf. MRC[5]). Some of the tools available to make up the package of prevention are reviewed below.

Currently available tools for HIV prevention

There is increasing evidence of the effectiveness of **male condoms** in preventing HIV infection.[6] From longitudinal cohort studies with sero-discordant couples the effectiveness of male condoms has been *estimated* at approximately 80%, but their precise degree of protection is unknown owing to complexities that make randomised controlled trials (RCTs) of efficacy unethical.[7] The **female condom** is currently the only available female-initiated prevention method and has also been estimated to be highly effective in preventing HIV infection.[6]

Education and risk-reduction counselling is a key component of HVTs.[8] However, while some studies suggest that behavioural risk-reduction interventions are effective in reducing risk behaviours,[8] none demonstrate significant reduction in HIV infection rates.[3] Data from community randomised trials on the impact of **STI treatment** on HIV infection are mixed. An initial study reported a significant decrease in HIV when STIs were treated through syndromic management, but subsequent trials found no effect on HIV.[6] For ethical and logistic reasons, RCTs of **non-occupational PEP** are unlikely to be conducted.[9] However, data from animal transmission models and observational studies suggest that non-occupational PEP 'might sometimes reduce the risk for HIV infection after nonoccupational exposures'[9] (p. 2).

Sharing contaminated needles is a major driver of HIV infection among injection drug users (IDUs). RCTs and case studies have shown that **drug substitution therapy** is effective in preventing the transmission of HIV among IDUs.[10] While RCTs of needle exchange programmes may not be feasible, evidence suggests that access to **sterile injecting equipment** is effective in preventing HIV transmission.[10] Three RCTs conducted in Africa indicated that circumcision at least halves a man's risk of contracting HIV through heterosexual sex. The **male circumcision** trial conducted in Orange Farm, South Africa, was stopped early after an interim review of data revealed that circumcision decreased the chances of acquiring HIV by 60%.[11] Studies in Kenya and Uganda to assess the applicability of the South African findings in other contexts were also halted after interim data suggested a 'highly significant reduced risk of HIV seroconversion among the men randomly assigned to circumcision'[11] (p. 568).

Complexities of providing proven/established effective tools

It is not clear when a prevention method is considered 'proven' or 'established effective'. While RCTs are considered the gold standard for establishing the efficacy of interventions, most of the currently accepted effective HIV prevention tools (e.g. condoms) were not subject to such rigorous testing.[12] An 'established effective' intervention has been defined as one which *is accepted by the international medical profession* as being as successful as any intervention in addressing an issue; however, consensus among experts is difficult to achieve and evaluate.[13]

Additionally, there are omissions from, and contradictions in, key ethical guidelines. Examples include that male circumcision receives no discussion as a recommended risk-reduction method under the guidance point on standard of prevention in the UNAIDS-WHO[2] guidelines. These same guidelines recommend that risk-reduction counselling possibly be provided by an independent agency owing to concerns around conflict of interest;[2] however, other prevention services apparently do not raise such concerns. Also, the UNAIDS-AVAC[14] guidelines set a very high procedural standard, including that researchers should *consult* with stakeholders, *document* the consultations, *map* service providers that will support sites, *build capacity* to do so, and *monitor* uptake of prevention services. Trials should also *not* be conducted in circumstances when 'agreements have not been reached among all research stakeholders on [the] standard of prevention'[2] (p. 13).

Furthermore, there has been little empirical investigation of the prevention services provided to participants in HVTs. More attention has been paid to microbicide and diaphragm studies where three South African sites have been researched.[15] It was found that participants do receive intensive quality counselling, unlimited free male condoms and quality STI services; however, female condoms were not actively promoted by site staff.[15] There has also been little comparison of how ethical guidelines correspond with actual practice at HVT sites or with the actual dilemmas experienced by researchers.

Recommendations for addressing complexities with providing currently available tools

1. Guidelines must be formally evaluated to highlight where guidance is least clear, to bring the most relevant guidance to the foreground, and to clarify researchers' responsibilities.
2. Prevention services offered to HVT participants, as well as decision-making practices, should be assessed.

3. It should be assessed whether practices correspond with ethical guidelines, and whether ethical guidelines provide direction on researchers' actual dilemmas.

Obligation to add new methods

Current *international* ethical guidance asserts that researchers, research staff and sponsors provide new methods to trial participants when they are 'scientifically validated or approved by the relevant authorities'.[2] Researchers must spell out how 'enhancement' of the package will be negotiated, considering factors such as feasibility, expected impact, and ability to isolate the efficacy of the new modality being tested. *South African* guidance states that new methods are added as they are 'discovered and validated'.[5]

What new methods could become part of the prevention package?

Pre-exposure prophylaxis (PrEP). Researchers are trying to determine whether antiretroviral drugs (ARVs) used to treat HIV/AIDS could be used as a prevention strategy. Currently four clinical trials are testing the safety and efficacy of PrEP with ARVs for HIV prevention. Tenofovir trials are being carried out among HIV-uninfected men who have sex with men (MSM) and IDUs. Results are expected in 2009 and 2010, respectively.[4] The PrEP candidate Truvada is being clinically tested in large-scale multicentre efficacy studies with MSM and with heterosexual men and women. Results are expected in 2010 and 2011, respectively.[4] An efficacy study is also comparing the effectiveness of tenofovir with Truvada in serodiscordant heterosexual couples. Results are expected in 2012.[4] To date, one trial of PrEP has been completed in Ghana with women, but showed no significant differences in infections between those who used PrEP and those who used placebo. Two trials of tenofovir were stopped in Cambodia and Cameroon because of ethical controversies.

Microbicides. Microbicides are female-initiated products applied to the vagina to prevent HIV infection. No microbicide products tested in efficacy trials (e.g. Carraguard, cellulose sulphate) have proven effective in reducing the risk of HIV infection.[6] The results of the phase II HPTN 035 trial became available in early 2009, and demonstrated that while BufferGel did not reduce HIV risk among women, PRO 2000 gel reduced risk by 30%.[16] However, these results were not statistically significant.[16] The phase III trial of PRO 2000 results will be released later in 2009 and will provide additional evidence to conclusively determine whether PRO 2000 prevents HIV infection in women.[16] The results of the phase IIB trial of tenofovir gel will be available in 2010.

Behavioural interventions. A behavioural RCT, Project UNITY, is currently underway. It compares enhanced HIV risk-reduction and vaccine education interventions with standard interventions used in HVTs.[4] Results are expected in 2009.[4]

Complexities of adding new tools to the package of prevention

The level of evidence needed for new methods seems to surpass what is accepted for current tools.[6] When adding new tools to the prevention package, researchers will need to consider the strength of evidence generated from the efficacy trial and the degree to which results can be extrapolated to other populations and contexts.[17] Specifically, researchers will need to assess the conclusiveness of the data, the need for further confirmatory trials, and the safety profile of the candidate product.[18] There is no set standard for this task. For example, researchers in the HVTN 503/Phambili trial decided to offer circumcision to male participants as part of risk-reduction counselling and the standard of prevention based initially on results of the South African trial, while WHO/UNAIDS cautioned that further research was needed to confirm the reproducibility and general applicability of these findings.[12] However, the initial decision to provide circumcision to trial participants was strengthened by the results of two additional trials which became available before HVTN 503 commenced.

Also, several regulatory complexities may exist. Some new prevention technologies must be approved by national regulatory authorities to be used in a country (e.g. PrEP researchers will need to initiate a change of indication with the Medicines Control Council (MCC)); others (e.g. circumcision) will not. Furthermore, for some products licensure requirements may be unclear, e.g. there was some debate regarding how to proceed should acyclovir have shown to decrease HIV infection by suppressing herpes simplex virus type 2 (HSV-2). From one perspective acyclovir was already approved and licensed for the treatment of herpes; therefore if it was found effective in preventing HIV infection, it would not need to be approved/licensed again. However, from another perspective it was argued that acyclovir has an anti-HIV effect[19] that may have explained any decreases in HIV transmission, therefore requiring researchers to apply for a change of indication. Some regulatory authorities have not outlined their requirements for licensure of products such as microbicides or vaccines. However, regulators often require that to be licensed, new products must be tested in at least two RCTs or a single pivotal trial (phase III trial) that provides as much evidence of effectiveness as two trials would have.[20] However, for interventions that are not medicines or devices, a national 'approval' process is less defined, e.g. it is not clear whether government's lack of objection to an intervention would constitute approval or whether active endorsement or policy development would be required. Furthermore, once regulatory obstacles are overcome, manufacturing, distribution and surveillance capacity may become important considerations.

Furthermore, ethical guideline requirements that trials should *not* be conducted without consensus among all

research stakeholders on the standard of prevention[2] may not adequately take into account how difficult consensus-building can be, that canvassing the opinion of affected parties may be morally relevant but not morally definitive,[21] and that in some instances this procedural requirement may serve to lower the substantive standard that such a package be 'state of the art'.

Lastly, when new tools are added to the standard of prevention, the incidence of HIV in large-scale late-phase trials is likely to decrease. When incidence is reduced, the statistical power of the study to detect significant differences decreases, making it increasingly difficult to demonstrate the efficacy of the candidate product.[20] In fact, a high uptake of the prevention package was offered as a possible explanation of the reduced power of the MIRA diaphragm trial.[15] Trials will therefore have to enrol more participants, and as trial size increases, so does the length and costs. For example, a study requiring 100 HIV infections with a 30% effective prevention package will require 4 866 participants to have sufficient power to detect significant effects. This increases to 8 515 participants when the package becomes 60% effective.[12] Such complications pose challenges for the development of more (and potentially *more effective*) prevention tools. When the addition of new tools will invalidate trial results or otherwise make trials impossible to run, then arguably the obligation to provide all such tools to participants is weakened. This is because invalid trial results mean that participants will have been exposed to risks for no purpose in that important societal knowledge for future beneficiaries will not be gained. In our view this is the ethical crux of the matter. Efforts[12] to thoroughly explore this concern need to be strengthened.

Recommendations for addressing complexities with adding new tools to the prevention package

1. There should be an expert consultation by HVT researchers, sponsors, regulatory authorities, community representatives and ethics committees to define the acceptable level of effectiveness to add new tools to the prevention package. Also, the threshold at which adding new tools will invalidate trial results should be explored.
2. Efforts should be made to understand how decisions are (and will be) made to add new tools to the prevention package offered to HVT participants.
3. Developing country regulators should outline their requirements for the licensure of new products.[8]
4. Sponsors and international donors should consider how trial budgets will be expanded to take into account new prevention technologies.

Conclusions

There has been little empirical exploration of what prevention services researchers currently provide to participants in HVTs, how they make decisions about what to provide, and their challenges and successes. Data are also limited on the degree to which service-delivery and decision-making practices correspond with standards in ethical guidelines. Empirical research is needed to fill this gap. Furthermore, new and promising results of products such as PRO 2000 gel plus the imminent possibility of positive results for PrEP or behavioural interventions indicate that HVT researchers must deliberate now about the implications for the prevention package offered to trial participants.

HAVEG is funded by the South African AIDS Vaccine Initiative. The views expressed here do not necessarily reflect those of SAAVI. We gratefully acknowledge helpful comments from Helen Rees, Sinead Delany-Moretlwe and Earl Burrell on issues related to regulatory challenges for new prevention tools.

References

1. Stover J, Fahnestock M. *Coverage of Selected Services for HIV/AIDS Prevention, Care, and Treatment in Low- and Middle-income Countries in 2005*. Washington, DC: Constella Futures, POLICY Project, 2006. http://www.futuresgroup.com/Documents/3482HIVCoverage2005.pdf (accessed 31 January 2007).
2. UNAIDS-WHO. *Ethical Considerations in Biomedical HIV Prevention Trials*. Geneva: UNAIDS, 2007. http://data.unaids.org/pub/Report/2007/jc1399-ethicalconsiderations_en.pdf (accessed 20 February 2008).
3. Lagakos SW, Gable AR. Methodological challenges in biomedical HIV prevention trials. 2008. http://www.nap.edu/catalog/12056.html (accessed 26 August 2008).
4. AIDS Vaccine Advocacy Coalition. Px wire: A quarterly update on HIV prevention research. 2008. http://www.avac.org/pxwire/2008/oct-dec.pdf (accessed 8 January 2009).
5. Medical Research Council. Guidelines on ethics for medical research: HIV/AIDS preventive vaccine trials. 2003. www.mrc.ac.za/ethics/ethicsbook5.pdf (accessed 17 June 2006).
6. Padian NS, Buvé A, Balkus J, Serwadda D, Cates Jr W. Biomedical interventions to prevent HIV infection: Evidence, challenges, and way forward. *Lancet* 2008; 372: 585-599.
7. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Systematic Review* 2002; 1: CD003255.
8. IAVI. Understanding risk-reduction counseling. *VAX* 2005; 3(8): 1-4.
9. Centers for Disease Control and Prevention. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: Recommendations from the US Department of Health and Human Services, 2005. http://www.aidsinfo.nih.gov/ContentFiles/NonOccupationalExposureGL_PDA.pdf (accessed 3 September 2008).
10. Valdiserri RO, Ogden LL, McCray E. Accomplishments in HIV prevention science: Implications for stemming the epidemic. *Nat Med* 2003; 9(7): 881-886.
11. Weiss HA, Halperin D, Bailey RC, Hayes RJ, Schmid G, Hankins C. Male circumcision for HIV prevention: From evidence to action? *AIDS* 2008; 22: 567-574.
12. Global Campaign for Microbicides. *Meeting Summary: Next Generation HIV Prevention Trials Working Group, 8- 9 November, 2007*. Washington, DC: GCM, 2007.
13. National Bioethics Advisory Commission. *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*. Bethesda, Md: NBAC, 2001.
14. UNAIDS-AVAC. Good participatory practice guidelines for biomedical HIV prevention trials. Geneva, 2007. http://www.avac.org/gpp.htm (accessed 3 April 2008).
15. Heise L, Shapiro K, West Slevin K. Mapping the standards of care at microbicide clinical trial sites. PATH, 2008. http://www.global-campaign.org/clientfiles/SOC.pdf (accessed 12 January 2009).
16. Microbicide Trials Network. Trial finds microbicide promising as HIV prevention method for women. 2009. http://www.mtnstopshiv.org/node/765 (accessed 12 February 2009).
17. van de Wijgert J, Jones H. Challenges in microbicide trial design and implementation. *Stud Fam Plann* 2006; 37: 123-129.
18. AIDS Vaccine Advocacy Coalition. AIDS vaccines: The next frontiers. 2006. http://avac.org/pdf/reports/2006_Report/AVAC_Report_2006_single.pdf (accessed 18 January 2007).
19. McMahon MA, Siliciano JD, Lai J, *et al*. The antiherpetic drug acyclovir inhibits HIV replication and selects the V75i reverse transcriptase multidrug resistance mutation. *J Biol Chem* 2008; 283(46): 31289-31293.
20. Heise LL, Wood SY. Rethinking the ethical roadmap for clinical testing of microbicides. 2005. http://www.global-campaign.org/researchethics.htm (accessed 29 January 2007).
21. Grady C, Wagman J, Ssekubugu R, *et al*. Research benefits for hypothetical HIV vaccine trials: The views of Ugandans in the Rakai District. *IRB Ethics & Human Research* 2008; 30(2): 1-7.

Accepted 7 July 2009.