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

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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.

Background, aims and methodology

Preventing new HIV infections is critical. However, less than one in five people has access to proven prevention methods, and 'for every person placed on antiretroviral treatment in 2006, another six people became newly infected with HIV'. Efforts to utilise existing prevention strategies better, and to identify new ones, are therefore imperative.

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.

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.

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Current ethical guidelines articulate that participants should receive access to preventive methods, later described as ‘optimal’ (p. 28) (our emphasis throughout the above paragraph).
UNAIDS-WHO 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). 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. 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. 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. Education and risk-reduction counselling is a key component of HVTs. However, while some studies suggest that behavioural risk-reduction interventions are effective in reducing risk behaviours, none demonstrate significant reduction in HIV infection rates. 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. For ethical and logistic reasons, RCTs of non-occupational PEP are unlikely to be conducted. 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. 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. While RCTs of needle exchange programmes may not be feasible, evidence suggests that access to sterile injecting equipment is effective in preventing HIV transmission. 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%. 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’ (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. 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.

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 guidelines. These same guidelines recommend that risk-reduction counselling possibly be provided by an independent agency owing to concerns around conflict of interest; however, other prevention services apparently do not raise such concerns. Also, the UNAIDS-AVAC 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’ (p. 13).

Furthermore, there has been little empirical investigation of the prevention services provided to participants in HVTs. More attention has been paid to microbiode and diaphragm studies where three South African sites have been researched. 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. 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’. 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’.

**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. 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. An efficacy study is also comparing the effectiveness of tenofovir with Truvada in serodiscordant heterosexual couples. Results are expected in 2012. 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. 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%. However, these results were not statistically significant. 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. 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. Results are expected in 2009.

**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. 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. 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. 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. 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 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. 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
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 at 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 200 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.

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References