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African AIDS Vaccine Program Satellite Session Report: *Revisiting ethical issues in preventative HIV vaccine trials in light of the early closure of the STEP and Phambili trials*

2008

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Preparation of this report received financial support from the WHO-sponsored AAVP based in Geneva, Switzerland. The ELH Collaborating Centre is an expert ethical advisory body to AAVP, established to provide independent advice to AAVP through WHO/IVR/HVI regarding the development of AAVP research ethics. WHO/IVR/HVI and WHO/AFRO/ATM also provide secretarial and administrative support to AAVP. The above financial support notwithstanding, the views expressed are those of the author and do not represent the views of any of the organizations listed above.

Title:	Revisiting ethical issues in preventative HIV vaccine trials in light of the early closure of the STEP and Phambili trials
Date:	2 December 2008, 14.00-17.00pm
Venue:	Ninth Global Forum on Bioethics in Research, Auckland, New Zealand
Apologies:	Dr Reidar Lie and Dr Zarifah Reed
Presenters:	Prof Douglas Wassenaar and Ms Nicole Mamotte
Commentary:	Dr Joseph Millum
Rapporteurs:	Ms Zaynab Essack and Ms Jennifer Koen

Background

On 13 October 2008, the Ethics, Law and Human Rights Collaborating Centre of the African AIDS Vaccine Programme hosted a satellite session on the 'Post STEP/Phambili Ethics Landscape' at the *AIDS Vaccines 2008 Conference*, Cape Town, South Africa, to provide stakeholders with an opportunity to identify the ethical issues that emerged from the closure of these trials and identify how future trials might most appropriately respond to similar issues.

Aims

The purpose of this follow-up session was 1) to report on the ethical concerns identified at the October meeting and to identify how to take ethical concerns further. Global Forum participants were invited to further debate and identify additional concerns with regard to the potential impact of the STEP/Phambili results on current ethical norms and standards.

Prof Douglas Wassenaar, Principal Investigator of the AAVP's Ethics, Law and Human Rights Collaborating Centre, opened the meeting and welcomed delegates.

Background: STEP and Phambili trials (Prof Douglas Wassenaar, AAVP ELH)

In his overview of the STEP and Phambili trials, Prof Wassenaar briefly described the AAVP and noted that the ethical implications of STEP/Phambili closure had not been adequately addressed to date. HIV prevention trials have raised enormous international debate in terms of standard of care (SoC); standard of prevention (SoPrev); consent (Voluntariness; testing understanding); and vulnerable populations. These trials are complicated because research is conducted on healthy volunteers. To this end, HIV vaccine trials are sufficiently complex to warrant HIV vaccine trial specific ethical guidance, e.g. UNAIDS (2007). South Africa and Kenya have also published guidance documents. However, the STEP and Phambili trials may reveal gaps and omissions in existing guidance or issues not adequately covered by existing guidelines.

Prof Wassenaar then provided some background information on the halted STEP and Phambili trials. They were Phase IIb (test of concept), double-blinded randomised controlled trials. The Ad5 vector was used as the delivery mechanism for synthetically produced HIV genes (gag, pol, nef). The vaccine targeted clade B strains of HIV. The aim of the trials was to determine whether the Merck vaccine candidate 1) prevents HIV infection and/or 2)

lowers the viral load in participants who become HIV infected. It was noted that, at this point in vaccine research and development, the focus of trials is on disease modulation because sterilizing immunity is unlikely, although ideal. The STEP trials were conducted in North and South America and Australia primarily with men who have sex with men (MSM) and injection drug users (IDUs). Interim unblinding of results by the Data Safety and Monitoring Board (DSMB) led to the trial being halted because the vaccine did not prevent HIV infection or reduce viral load among participants who became HIV infected. In addition there were more HIV infections in the vaccine arm (n=49) compared to the placebo arm (n=33). This suggests that participants who received the vaccine had enhanced susceptibility to HIV infection compared to those who received the placebo. Importantly the vaccine did not *cause* HIV infection. For infection to occur there had to be exposure to HIV through risk behaviour. *Post hoc* tests have indicated that uncircumcised Ad5 seropositive men were more likely to have enhanced susceptibility to HIV. However these data are complicated both statistically and technically. Therefore results should be interpreted cautiously as the study was not stratified to look at effects of circumcision. In addition, people with high Ad5 immunity were less likely to be from the US or Australia. This raises the question of whether the results reflect a genetic difference in susceptibility or response to the vaccine, and whether natural immunity to Ad5 is an epiphenomenon. Follow-up of participants suggests that there was no statistically significant difference in viral loads between groups; this suggests that participants in the vaccine group are no worse off than those in the placebo group in this regard. Those infected in both the vaccine and placebo groups also began ART regimens at similar times.

The Phambili trial was conducted in South Africa. The mode of transmission in South Africa is primarily heterosexual intercourse. Given that the predominant clade in South Africa is clade C and the vaccine was designed for a clade B population, this trial was politically sensitive; however the study was accepted given the enormous burden of HIV in South Africa and the lack of successful preventive interventions to date. Across South African sites, 801 of the anticipated 3000 participants were enrolled; 400 of whom were randomised to the vaccine arm. By design, 50 percent of participants were female. This trial was halted in September 2007 in light of the STEP interim results. Participants were unblinded in October 2007. Follow-up is ongoing and there have been no new HIV infections post-unblinding up to December 2008. This is behaviourally interesting finding in itself. The results are similar to the STEP results although fewer participants had received 3 doses of the vaccine. In the Phambili trial 7% received 3 vaccines, 66% received 2 vaccines and 17% received 1 vaccine. There were 29 seroconversions: 17 in the vaccine group and 12 in the placebo group; 7 were male and 6 of these 7 were uncircumcised. 40% of male participants in the Phambili trial were circumcised or opted to be circumcised. The majority of those who were HIV infected were Ad5 seropositive (26 of 29): 16 of 17 in the vaccine arm group and 9 of 12 in the placebo arm. The results do not indicate a statistically significant difference in the number of infections between vaccine and placebo but rather a trend towards enhanced susceptibility to HIV infection among participants in the vaccine group. These results are similar to the STEP results.

The Post STEP and Phambili Ethical Landscape (Ms Nicole Mamotte, AAVP ELH)
Ms Mamotte provided a report back on the outcomes of a n AAVP ELH satellite meeting held at the AIDS Vaccine Conference in Cape Town in October 2008. The meeting aimed to identify critical ethical issues emerging from the closure of the STEP and Phambili trials and how future trials might most appropriately respond to similar issues. The principal investigators of the STEP and Phambili trials, Dr Susan Buchbinder and Dr Glenda Gray respectively, presented at the satellite session as did Dr Ruth Macklin of the Albert Einstein College of Medicine, New York. Ms Mamotte acted as rapporteur for the satellite meeting in Cape Town.

Ms Mamotte outlined the aims of the Cape Town meeting which were to 1) inform stakeholders about the STEP and Phambili trials, 2) reflect on the STEP and Phambili trial results in light of the UNAIDS/WHO (2007) and UNAIDS/AVAC (2007) guidance documents, 3) identify ethical inputs and concerns, 4) raise awareness of the ethical norms that have been impacted by the STEP and Phambili trials and 5) identify how future trial protocols should anticipate and respond appropriately to such issues.

Ms Mamotte noted that the report would be structured according to the Emanuel et al (2000; 2004) conceptual framework. She described the eight principles of collaborative partnership, social value, scientific validity, fair selection of participants, favourable risk-benefit ratio, independent review, informed consent and ongoing respect for enrolled participants. She briefly outlined how the guidance points in the UNAIDS (2007) guidance document link with the principles in the Emanuel framework.

The remainder of her presentation focussed on reporting the ethical issues, challenges and recommendations identified in the satellite meeting. The first identified scientific validity issue considered whether the finding of enhanced susceptibility among vaccinees means that current vaccine approaches are too risky. It was noted that it is still ethical to proceed with clinical trials of vaccines but steps should be taken to minimize risks and future trial designs that include the probable suspected causes of enhanced susceptibility should be avoided. The second scientific validity issue was that using a Phase IIb, test of concept trial design was useful in these trials as it demonstrated that the vaccine candidate should not progress to Phase III trials, and therefore fewer participants were exposed to risk.

Issues identified during the Cape Town meeting in terms of fair subject selection included that enhanced susceptibility, particularly among uncircumcised Ad 5 seropositive men, was a critical consideration for future vaccine trials, especially with this vector. In addition all future Ad5 vaccine trials should include men that are Ad5 negative and circumcised. Secondly, an adolescent trial, Phambalini, was planned for South Africa had the interim results of the Phambili trial been promising, this highlights the importance of establishing safety in adults

first before products move into adolescent trials[1].

The need to maximize benefits was identified in the Cape Town meeting: benefits should not be limited to trial participants; benefits as contributions to scientific knowledge and benefits to others in the future were also identified. In terms of minimizing risks, strategies for identifying risks/harms early are needed as are strategies for continuous monitoring. Safeguards to prevent risks should also be put in place. It was noted that informed consent alone does not fulfil the researcher's obligation to minimize risk.

Independent review issues raised in the Cape Town meeting include that RECs and regulators are going to be asking harder questions. These questions however should be relevant to the protection of participants. There was concern that the STEP data safety and monitoring board (DSMB) interim analysis schedules were not known and that the results would not be made available to the study protocol team. It was also recommended that DSMB members should be identified publicly. An important lesson learnt in the STEP and Phambili studies was the need to be prepared for getting results early and to have strategies in place for dealing with early results.

Issues identified around informed consent in the Cape Town meeting included 1) how to ensure that participants in the trials were and continue to be informed about trial results, 2) how to ensure that future trial participants are truly informed and 3) what must be disclosed in the informed consent process in future trials? Issues to be disclosed include the fact that no trials of vaccine products to date have been efficacious, the potential for enhanced susceptibility and whether the vaccine product and risk factors in future trials are similar to those in the STEP trial. It was also noted that informed consent is a process and not just a form and that tests of understanding are particularly pertinent.

Finally, issues involving communicating results, access to treatment and standard of prevention identified in the Cape Town meeting were discussed. In terms of communicating results, the need to contact participants quickly was identified. This should be within 72 hours and before widespread press coverage. Radio broadcasts and bulk text messages are useful strategies. REC approval was required for all standardized communication with participants and therefore RECs should pre-approve communications in advance. Communicating complex negative results to the public requires a basic level of research literacy. In her report of access to treatment, Ms Mamotte outlined the care and treatment guidance point in the UNAIDS (2007) guidance document which states that participants who are infected with HIV should be provided with access to treatment and that stakeholders including communities should decide on the mechanisms to provide and sustain HIV-related care and treatment. She also discussed whether the enhanced susceptibility among vaccinees in the STEP trial can be considered a trial-related harm. She reported that

[1] WHO/UNAIDS/AAVP International Expert Group. (2007). Executive summary and recommendations from WHO/UNAIDS and AAVP consultation on: 'The inclusion of adolescents in HIV vaccine trials', 16–18 March 2006 in Gaborone, Botswana. *AIDS* 21, 1–10

enhanced susceptibility presents an "enhanced obligation" to follow up and monitor participants and ensure access to ART. However it does not present an enhanced obligation to monetary compensation unless agreed on in advance. In terms of standard of prevention, Ms Mamotte discussed whether circumcision should be stipulated as an enrolment criterion for male participants in future trials or whether circumcision should merely be recommended/encouraged. She reported that if trials use circumcision as an inclusion criterion, they might discriminate against uncircumcised men and that there are important traditional and cultural considerations regarding circumcision. She noted that factors suspected to increase risk must be reduced in future trials.

Ms Mamotte concluded her report back by considering a way forward. She asked the group for feedback on the ethical issues, challenges and recommendations generated by the Cape Town meeting and for any additional ethical inputs, concerns and recommendations. She also asked the group to reflect on the appropriateness of the conceptual framework that was used to structure the issues and on how best to take these ethical concerns forward.

Commentary (Dr Joseph Millum, NIH)

In his commentary, Dr Millum made two requests for precision. First, to distinguish between substantive or procedural issues – is it about the broader ethical issues or are there procedures which should be changed or implemented? Second, who are the different stakeholders we want to address our claims to? Who should be responsible for what?

Dr Millum made several comments with regard to the use of the Emanuel et al (2004) framework. In terms of *scientific validity*, Dr Millum explained that questions relating to whether a vaccine is excessively risky are not issues of scientific validity as it is irrelevant to whether or not the research can answer the questions; rather it relates to social value or risk-benefit considerations. With regard to *social value*, Dr Millum highlighted that considerations of availability or effectiveness in the general population are important and that for further research with similar vaccines, there will need to be equipoise and scientific value. In terms of *favourable risk/ benefit ratio*, Dr Millum noted that people who have a stake in the vaccine should be able to consider/ have an input into what they would consider to be a fair risk/benefit ratio. They need to distinguish parties that endure risks and receive benefits. He emphasised that benefit to society can not be weighed against risk to individuals, risks that are too large to participants will not be outweighed by benefits to society. One needs to separate 'concrete' benefits and social goods. With regard to *informed consent*, because people generally, and vulnerable populations specifically, do not necessarily understand clinical trials, risks should be reduced and informed consent processes enhanced to ensure voluntariness.

When considering circumcision as a *standard of care* (SoC) or *standard of prevention* (SoPrev) Dr Millum emphasised that the issue of SoC is not well-captured by the Emanuel framework but that changing SoC has implications for scientific validity and social value. He also noted that raising the SoPrev by adding circumcision or making it an inclusion criterion

may move away from the population in which the vaccine will be used and will impact on generalisability. Therefore it will result in answering the wrong question, given what we want to do with the vaccine. In terms of a*ccess to treatment,* Dr Millum asked if we should be giving people access to treatment or care that people who were not in the trial would not have access to, simply because they were involved in the trial. These people were likely to become infected anyway because of the risky behaviour that they engage in. He also voiced his suspicion of the proposal of enhanced obligation to provide vaccinees with ART if they become HIV infected, can we really justify giving people different levels of 'benefit'?

Group Discussion

Several concerns and gaps were identified during the group discussion.

Circumcision: In STEP and Phambili the sample was stratified according to Ad5 and not circumcision, so circumcision data is *post-hoc* and statistically weaker, but shows a trend towards an effect. It was noted that introducing circumcision into the trial could create a gender bias in benefits. However, modelling studies indicate that there will be an indirect benefit to women as well. It was also noted that while cultural or religious factors may impact on the uptake of circumcision, it should still be offered to both arms.

Enhanced obligation: Enhanced obligation was felt by some to be a good theoretical concept but pragmatically difficult to take into consideration or to establish until the end of the trial – if it is due to uncertainty about the result then it strengthens obligations to provide treatment and care. It was also questioned whether 'enhanced obligation' is something new or a 'cranking up' of existing ethical obligations?

Access to treatment: The debate about treatment and care is about whom should be responsible. Access to care and treatment must be guaranteed. It is a criterion on which trials might be turned down. Researchers cannot merely say that it will be provided, there need to be some procedures in place to ensure access to treatment. However, there is no guidance on who should provide access to treatment or how this should be done.

Risks and benefits: In general, trials are conducted with low-risk populations before more vulnerable groups – but people do not generally understand risk. Studies should be designed to reduce risk but given the nature of HIV mutation and the urgency of the problem, there is also a need to enrol people and test as many products as possible. This reflects a tension between need for rapid progress and caution. It was also noted that there are different benefits and risks to different groups - we therefore need to consider benefits/risks to 'the reasonable person'. While it may not be possible to determine what would be appropriate for each group, a general level is possible to determine and this is routinely done by RECs regarding individual risk.

The difficulty of comparing risks and benefits was discussed. Some participants felt that often risks to one group are compared with benefits to a different group; therefore there is a need

for intra-stakeholder analysis where risks and benefits are catalogued for each stakeholder group. It was suggested that risks and benefits should be considered separately. It was noted that risks/benefits and fair benefits to participants and communities are separate issues. If benefits are discussed in connection with risks then some felt they could be an inducement. As people who participate in trials do so for a variety of reasons, some thought the risk-benefit debate is a false debate.

On the other hand others felt that although risk/benefits are difficult to compare we do it all the time. Risks to individuals must be justified (in addition to individual benefits) by a broader societal benefit. The point of doing research is to generate interventions that are valuable to others outside the trial. If beneficial to participants, this is an added bonus. When there is genuine equipoise benefits to the participants should not be expected, if benefits were expected there would be no need to conduct the trial.

Standard of Care: Whether the standards of care provided to participants at different sites or in different countries can be compared was questioned.

Science: The following questions were raised regarding the science of vaccine trials. Is there justification for having a third arm which includes just the vector? The control group in Malaria vaccines is often a vector-only arm. Do we know what Ad5 does to natural HIV-infections?

Convergence: The importance of convergence both across and within fields, e.g. malaria and TB trials; vaccines, PreP and microbicides was noted. Difficulties with funding were highlighted, funds are likely to be allocated to a specific problem but it was still felt that convergence is a valuable aim. It was felt to be in sponsor's interests to cut across different disease entities as this allows for the sharing of resources which are frequently scarce in developing country settings. Convergence between fields may also shed light on thresholds for risks and benefits. We could also learn how to cope with crises like STEP/ Phambili from other fields which may have experienced similar issues e.g. microbicides

Research ethics committees: The capacity of ethics committees to address all of the complex issues raised by the STEP/Phambili studies was questioned. It was noted that RECs (not just in developing countries) frequently experience difficulties or lack of capacity when reviewing HIV Vaccine Trials[2]. It was noted that there is sometimes pressure on RECs in developing countries or of lesser standing to approve trials approved by more 'powerful' committees.

It was questioned whether research ethics committees should be reviewing the science as ethics and science are two separate issues? In response it was clarified that there may be numerous scientific options for answering a question but one may be more ethical than

[2]Milford, C., Wassenaar, D., & Slack, C. (2006). Resources and needs of research ethics committees in Africa: Preparations for HIV vaccine trials. *IRB: Ethics and Human Research, 28*, 1-9.

another so ethics and science cannot be separated out. The importance of REC approval and researcher capacity-building as well as RECs protecting the researcher in the case of things going wrong was noted. As good science often has negative results, RECs can back up researchers where ethically conducted trials have unexpected adverse outcomes.

DSMBs: Debate emerged around the role of DSMBs. The conduct of trials is intensely participatory and then an external, 'sterile' body closes the trial. In addition, DSMBs are also routinely paid by the sponsor. It was felt that ethics committees should be able to demand greater involvement in the interim analysis

Motivations to enrol: It was felt that more clarity was needed on why people enrol in such trials. Relationship between social science and normative ethics – social science data is relevant but not determinant. Research ethics Committees should consider social science data but to what extent; further, to what extent does the data represent the concerns of the community? Also, what obligation is there to change community practices which may be unethical?

Media and communications: Question about the role of the media were raised, such as when to involve the media. Researchers and RECs need to have access to allied and knowledgeable journalists who understand science and design issues so that crises are not sensationalised, preventing more social harms or unnecessary distress. There is an obligation for researchers and RECs to cultivate a) informed ethics awareness, b) staff competence and preparedness to deal with crises and to manage information which is transmitted to participants and communities, c) ways of dealing with bottlenecks and bureaucratic approvals which sometimes take time and leave staff in a situation where they don't know what to do.

Role of ethics: STEP/Phambili trials identified that ethicists and scientists need to work more closely. Ethics tends to theorise too soon –they need to know what actually happened during the course of the trial; what decisions were made and why. They need to think about the social consequences of the closure of these trials for participants, communities and society.

Relevance of Emanuel et al Framework: This framework treats issues as separate but there are issues which overlap, e.g. collaborative partnership has implications for informed consent. It was also felt that the framework leaves out a lot in terms of vaccine trials – it does not deal with ongoing treatment for duration of the trial or indemnification or what should be provided in the event of something going wrong

The session was closed by Prof Wassenaar who thanked the participants for their valuable contribution to the debate.

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Appendix 1: Participant List

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