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African AIDS Vaccine Program Satellite Session Report: *The Post STEP/Phambili Ethical Landscape*

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Title:	The Post STEP/Phambili Ethical Landscape
Date:	13 October 2008
Venue:	AIDS Vaccine Conference 2008, Cape Town, South Africa
Chairs:	Ms Cathy Slack and Mr Mitchell Warren
Speakers:	Dr Glenda Gray; Dr S Buchbinder; Dr R Macklin
Participants:	Attendees at the International AIDS Vaccine Conference
Rapporteur:	Ms N Mamotte
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Background

Many stakeholders are processing the implications of the HVTN 502 ("STEP") trial results, which indicated that firstly, the Merck vaccine candidate was not efficacious and secondly, may have enhanced the susceptibility of certain participants to HIV infection (Merck/ HVTN, 2007). The results of a sister trial which was closed early in South Africa, HVTN 503, ("Phambili") are also being analysed. The STEP trial provided the field with important answers (the candidate vaccine does not prevent infection or disease) and alerted the field to some significant concerns (the candidate may have not be safe for certain sub-groups of participants). As such, the trial is not a failure but rather has yielded information that is, on the one hand, critical but, on the other, disappointing and alarming for many stakeholders. Negative trial results are an opportunity for careful reflection on both scientific and ethical concerns. In this instance; ethical issues could include: community participation; collaborative partnerships; informed consent; assessment of risk behaviour; ethical or regulatory review; monitoring by DSMBs, access to treatment and care; or results dissemination.

This session was developed as an informal collaboration between the African AIDS Vaccine Program Ethics, Law and Human Rights working group (AAVP ELH), the World Health Organisation (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the International AIDS Vaccine Initiative (IAVI), the HIV Vaccine Trials Network (HVTN) and AIDS Vaccine Advocacy Coalition (AVAC).

Aims

The aims of the session were as follows:

(i) To inform participants about the STEP and Phambili trial results

(ii) To enable participants to reflect on the STEP and Phambili trial results in light of the two new UNAIDS/WHO (2007) guidance documents on *Good Participatory Practice* and *Ethical Considerations in biomedical HIV prevention trials*

(iii) To identify participants' ethical inputs and concerns

(iv) To raise participants' awareness of the ethical norms that have been impacted by the STEP and Phambili trials; and

(v) To assist AAVP and other relevant stakeholders to identify how future trial protocols should respond appropriately to such issues.

The session was opened by Ms Catherine Slack who introduced the speakers and outlined the aim and structure of the session, and introduced the speakers Dr G Gray (Perinatal HIV Research Unit (PHRU), Soweto); Dr Buchbinder (HIV Vaccine Trials Network (HVTN)) and Dr R Macklin (Albert Einstein College of Medicine).

Ethical concerns in HIV Vaccine Trials (HVTs): A view from STEP (Dr S Buchbinder)

Dr Buchbinder presented selected ethical concerns and lessons learned as a result of the STEP study. Dr Buchbinder began her presentation with some background information on the STEP study. There were 34 sites. The majority of participants (62%) were men (mostly MSM) and 38% were women. The interim analysis, conducted in Sept 2007, indicated that firstly, the Merck vaccine candidate was not efficacious and secondly, may have enhanced the susceptibility of certain participants to HIV infection. Particularly, Ad5-experienced and uncircumcised men appeared most at risk. These findings led the Data Safety and Monitoring Board (DSMB) to recommend that all immunisations be stopped. The Study Team, in collaboration with community members decided to unblind the study. Unblinding and public presentation of the results took place in Nov 07, but follow-up of study participants has continued to date to assess what happens to infection rates in women, and to examine if increased susceptibility to HIV infection remains or fades. Retention remains high with >89% in both arms. Dr Buchbinder outlined the three primary ethical issues they encountered as a result of the DSMB findings.

1. *Collaborative partnership: Communicating results*

The results of the first interim analysis were not expected, as such communicating study results created several challenges. The challenge was to contact participants quickly before widespread press coverage. The general public was notified within 72 hours of the DSMB meeting, and study sites needed to get regulatory approval before using standard written communication. Sites used a number of creative solutions to contact study volunteers quickly. A key lesson learned was the importance of planning ahead for negative trial results. Some sites now have a pre-approved letter from their IRB/REC to inform participants that they have new information on the study which is available on their website, to ensure that results can be communicated to participants quickly. Communicating complex results to the public was also challenging. It became clear that a basic level of research literacy in the general public was important.

2. *Informed consent*

The issue of how to ensure that participants in the STEP trial were (and are) informed

thoroughly about trial results, even as results are not well understood, emerged as a central ethical concern.
It is also a challenge to ensure that participants in other trials are informed about the STEP results and how that trial differs from the trial they are participating in. Such participants need some information but not so much as to "swamp" them. Consent is a process and not a form. Tests of understanding need to be included to ensure participants understand and they need to be reminded throughout the trial about key elements of the trial. There are additional complexities for studies with "low risk" participants.

3. *Review: Study monitoring and DSMBs*

The importance of DSMBs and challenges of handling early information were also evident. Study monitoring was scheduled for three times a year. The DSMB reviewed results and conducted an efficacy analysis at the first 30 infections. This was the first opportunity to see the increased risk of infection. In this study interim analysis schedules were not broadcast and the study protocol team were not expected to get results. This raised important questions around who should know about timing of interim meetings and who should know interim results. It also illustrated the importance of having strategies for identifying harm early and for continuous monitoring, particularly in early trials (which are smaller and therefore have more uncertainty). It also raises the question of whether DSMB members should be identified publicly. DSMB membership was originally kept confidential but there is now a move for DSMB members to be named on manuscripts.

Dr Buchbinder ended her presentation with a discussion of the lessons learned from the Step Study. Lessons learned were that transparency is critical; broad and quick communication with investigators, participants, and public is essential; each prevention trial impacts on all others; community is important at each stage of a trial and that study volunteers are critical to our search for an HIV vaccine. Importantly, trial investigators need to prepare (as best they can) for the unexpected, there is no way to know when there may be unexpected results.

Ethical considerations Post-Phambili (Dr G Gray)

Dr Gray began her presentation with a detailed discussion of the Phambili trial closure and unblinding. Dr Gray described how two phase IIB HIV vaccine trials using the Merck candidate (MRKad5 gag/pol/nef) were being conducted in two parts of the world. The HVTN 502/STEP study was conducted in areas of the world where the predominant HIV sub-type was B, and the major risk of acquisition was through MSM, IDU & heterosexual transmission. This study enrolled 3000 participants. The HVTN 503/Phambili study was conducted in South Africa where the predominant HIV sub-type is C, and the major risk of acquisition was heterosexual transmission. Phambili stopped immunizations and enrolment in September 2007 after the first STEP DSMB and only enrolled 801/3000 participants. Enrolment for the Phambili study

began in the first quarter of 2007 in five sites in RSA. Enrollment and vaccination ceased on 19th September, 2007 following the results of the first DSMB meeting of HVTN 502/STEP study where futility was declared. On the 19th September 2007: HVTN 503 had 801 enrolled (45% female): 58 participants had received 3 vaccinations, 501 had received 2 vaccinations and 215 had received 1 vaccination. The age range of participants was as follows: 18-20yrs: 30%; 21-30yrs: 60%; 31-35: 10%.

Ongoing respect for participants: Unblinding:
The Phambili DSMB met twice thereafter and recommended unblinding participants based on the data emerging from HVTN 502/STEP study. This was newsworthy in South Africa and managing communications was trying. The public had to be notified within 2 days of the cessation of enrolment/ immunization. In this time all stakeholders needed to be reached and they had to ensure that participants were contacted the before media released the results. The results were communicated to participants via phone, bulk SMS and radio, telling them to come into the sites or call the research staff – it was a challenge to alert participants, but not alarm them. In 3 days 200 participants were unblinded and in just over 7 days, 750 participants were unblinded. At the time of this presentation, 3 volunteers remained unblinded.

The Phambili DSMB reviewed the STEP data. They found there to be lack of efficacy for both endpoints and more infections in the vaccine than placebo arms. The STEP DSMB recommended no further immunization and Phambili DSMB concurred. The Phambili DSMB recommended suspending enrollment and study injections, unblinding participants, and counselling participants about possible increased risk of HIV infection, based on data from STEP.

Dr Gray outlined the HIV infections in Phambili before unblinding. There were 11 confirmed cases of HIV infection, prior to unblinding – 7 cases in the vaccine arm and 4 cases in the placebo arm. 10 cases of infection were in women and one male placebo recipient with a high Ad5 level (>18 units) was infected. Among the 7 vaccine recipients who became HIV-infected, 2 received only one vaccination, 4 received two vaccinations, and 1 received all three vaccinations.

The trial related issues pre-unblinding, identified by Dr Gray, were: dual protection for pregnancy, co-enrolment, remuneration, and co-morbidities. Trial related issues post unblinding were identified as: co-enrolment, withdrawal prior to completion of study, consent withdrawal and sero-convertors requiring ART. Dr Gray ended her presentation identifying the key ethical considerations that emerged form the Phambili trial as being how to balance risk-benefit concerns, exploring the merit of compensation for research-related injury (which she

identified as being a stakeholder concern unique to the local context), and ensuring access to treatment for HIV-infected participants as well as for other "ancillary" conditions like hypertension and diabetes.

Ethical Implications of STEP and Phambili (Dr R Macklin)

Dr Macklin discussed the ethical implications of the STEP and Phambili trials. She firstly identified the need to maximize potential benefits. Dr Macklin emphasized that ethical requirement to maximize benefits in clinical trials is not limited to trial participants; benefits may be to others in the future. She highlighted that contribution to scientific knowledge also counts as a benefit. If benefits to participants were a necessary ethical requirement, most research involving healthy volunteers could not be conducted, as in phase I studies risks to participants almost certainly outweigh potential benefits to them. Dr Macklin then discussed the need to take steps to minimize known risks. The problem however arises with unanticipated risks. Many risks cannot be anticipated in phase I studies. The relatively small numbers of participants means that some risks will not be detected. Dr Macklin addressed the issue of enhanced risk to some STEP participants. A subgroup of participants in the experimental arm of the STEP trial were found to have higher incidence of HIV infection than participants in the placebo arm, especially men who were uncircumcised and had pre-existing immunity to the AD5 vector. She argued that identifying this increased risk was critical in order to avoid similar results in future HVTs. Dr Macklin argued that the phase IIB, test of concept trial design was advantageous (a reverse benefit) in this case because it determined that this vaccine candidate should not go to phase III, the alternative would have been a large-scale phase III trial and more participants would have been placed at risk in the larger trial.

Dr Macklin raised several important questions about the future of HIV vaccine trials. Do these results mean that HIV preventive trials in humans should not continue? Does the finding of enhanced susceptibility among participants who received the vaccine mean that current vaccine approaches are too risky (and therefore unethical)? She argued that as long as measures are undertaken to reduce risks to a minimum, it is still ethical to proceed. For example, the trend to greater number of infections among uncircumcised men in the vaccine group suggests that circumcision should be explicitly encouraged, a more debatable issue is whether lack of circumcision should be an exclusion criterion.

In terms of access to treatment for HIV infection, Dr Macklin introduced the Care and Treatment guidance point in the UNAIDS/WHO (2007) *Ethical Considerations in HIV biomedical trials*. Participants who acquire HIV infection during the conduct of a biomedical HIV prevention trial should be provided access to treatment regimens from among those internationally recognized as optimal. Prior to initiation of a trial, all research stakeholders

should come to agreement through participatory processes on mechanisms to provide and sustain such HIV-related care and treatment. Dr Macklin reflected on the implications of this guidance point for people who acquire HIV during a trial. In the past, many argued whether participants who become infected in trials through their own behaviour should receive treatments to which non participants do not have access. Dr Macklin questioned, if there was enhanced susceptibility for those who received the vaccine, whether this was a trial related harm. She argued that it was trial related harm, and that it arguably calls for an "enhanced obligation" to follow up and monitor participants and ensure them access to ART (arguably for longer than some agreements have done). Dr Macklin argued that some commitment is better than none but with trial related harm there should be no limit on treatment access time-periods. With regard to monetary compensation for trial-related injury, she argued that it is only necessary if stipulated in advance.

In addition, the negative results should now be disclosed in the informed consent process. Absence of efficacy in past trials needs to be communicated to future participants. Facts regarding enhanced susceptibility of participants in the STEP trial and how the trial products and design differ from STEP/Phambili should probably also be communicated in future trials information sheets.

Dr Macklin concluded by saying that there is every good scientific and ethical reason to proceed with future clinical trials of preventive HIV vaccines. However, it would be unethical to embark on future trials where the same risk factors found in the STEP trial are present. The ethically best course of action would be to avoid future trial designs that include the probable suspected causes of enhanced susceptibility as suggested by the STEP data. Yet uncertainties remain and vaccine researchers should use all available evidence when making decisions under risk and uncertainty.

Questions and Answers

During the Question and Answer session, a number of concerns were discussed.

Subject selection: Adolescent Participation: It was questioned *w*hat the findings from the STEP and Phambili trials mean in terms of future adolescent enrolment in HVTs. It was explained that hyper-vigilance is necessary and that there is unlikely to be any adolescent enrolment in the next couple of years, because the post-STEP legacy will be that evidence is needed from adults first that vaccines do not enhance HIV acquisition risk, before moving into adolescents.

Risk – benefit issues: The relative contribution of the vaccine in acquisition of HIV was questioned. It was clarified that men who were uncircumcised, were AD5 positive, and who received the vaccine had a higher rate of sero-conversion. However, other factors that may

explain the increased HIV acquisition are still being explored (e.g. co-infection with HSV). It was noted that investigations currently are underway to explore if pre-existing immunity caused a differential response to the vaccine at the mucosal level.

It was questioned whether male participants in future HIV vaccine trials will have to be circumcised, or if this should merely be recommended. On the one hand it was noted that if trials apply circumcision as an exclusion criteria, this might discriminate against uncircumcised men. The benefits of circumcision for MSM are not that clear, and it takes the choice away from participants. It was argued, however, that the Merck trial data means that factors suspected to increase risk (e.g., lack of circumcision and MSM) must be reduced in future trials, in order to preserve equipoise. In addition, it was noted that relying on informed consent is not sufficient to adhere to obligations to minimise risk, and additional steps must be taken. It was also questioned what the implications for HVTs will be if Prep is found to be effective and how it will be possible to reach endpoints in HVTs. In response, it was clarified that if re-exposure prophylaxis (Prep) is found to be efficacious it will be offered and trials will be designed to incorporate higher standards of prevention.

Ethics and Regulatory Review: It was questioned whether RECs and regulators are going to be asking harder questions and if one could conclude that they are going to make application procedures more stringent. In response, it was clarified that what is important is that RECs and regulators ask questions relevant to the protection of participants and that they ensure that safeguards are built into trials to prevent risks and plan for negative outcomes.

Ongoing respect for participants: Compensation for research-related injury: It was questioned why non-industry sponsored research does not require compensation plans to be built into trials while every industry sponsored clinical trial has a compensation plan and clear policies for compensation. In response, it was clarified that all investigational research in South Africa needs insurance for it to be approved by the Medical Control Council (MCC). Therefore all trials in South Africa , including HIV vaccine trials, have insurance policies regardless of sponsor. Dr Gray suggested that the audience view the *AIDS Vaccine* conference poster on compensation in the Phambili trial by Koen et al (2008)[1]. It was further added that trial related harm is not easy to determine and it is difficult to meet the criteria for compensation stipulated in the policies. It was also noted that STEP and Phambili did excellent work in terms of communicating negative results during the trial closures.

The session was closed by Mitchell Warren.

[1] Koen, J., Slack, C., Essack, Z., & Barsdorf, N. (2008). Payment of trial participants can be ethically sound. But how to move past a flat rate? Poster presentation at the AIDS Vaccine Conferece, 2008, Cape Town, South Africa

Conclusion

HIV prevention trials have raised enormous international ethical debate. These trials are further 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. the UNAIDS/WHO (2007) guidance document on *Ethical considerations in biomedical HIV prevention trials.* This session provided stakeholders with an opportunity to identify the ethical concerns emerging from the closure of the STEP and Phambili trial and to reflect on the trial results in light of the two new UNAIDS/WHO (2007) guidance documents. In doing so gaps and/or issues not adequately covered by existing guidance points were revealed. The primary UNAIDS/WHO (2007) guidance points implicated were: potential harms and benefits; scientific and ethical review, informed consent; standards of prevention; care and treatment and availability of outcomes.

Way forward

This report will be circulated to participants and the session will be reported on at an AAVP ELH satellite session at the 9th Global Forum on Bioethics in Research in Auckland, New Zealand on 2 December 2008. The purpose of this follow up session is to report on the ethical concerns identified at the October meeting and to identify how to take ethical concerns further. Global Forum participants will be 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