

Ethical-legal concerns in adolescent microbicide & HIV vaccine trials

Report on an international consultation held in Durban, South Africa, September 5-6, 2007.

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1 EXECUTIVE SUMMARY

Adolescents around the world are at risk of HIV infection. Of 3.5 million new infections in 2003, about 700 000 occurred in persons below 15 years. Adolescent girls are particularly vulnerable to HIV infection. Thus young persons are deserving beneficiaries of safe, effective HIV prevention products such as vaccines and microbicides. To ensure safe and effective products are available for this much-affected group, they must be enrolled in trials. However, there are a number of complex ethical and legal challenges.

The published literature has outlined many ethical-legal concerns; and prior consultations have reached for consensus on standards for adolescent trials. Notwithstanding, there has been limited work to develop resources to help stakeholders resolve difficulties at a local or international level. In addition, few consultations have explicitly tried to share complexities and experiences across the fields of vaccines and microbicides.

A forum funded by PATH through the Global Campaign for Microbicides (GCM) was held in Durban, South Africa on September 5th and 6th 2007. The forum was hosted by the HIV AIDS Vaccines Ethics Group (HAVEG). It brought together stakeholders in HIV vaccine and microbicide trials who were planning or implementing adolescent participation, including sponsors, investigators, community and government representatives, civil society organisations, and legal and ethics experts.

The forum aimed for a detailed analysis of adolescent complexities common to both fields, from 4 viewpoints, namely (i) Community (C) (ii) Science (S) (iii) Ethical (E) and (iv) Legal/Regulatory (LR). It also aimed to identify steps and resources needed to move the adolescent agenda forward.

Lori Heise (GCM) opened the meeting and Catherine Slack (HAVEG) presented the hopes for outcomes for the meeting.

In the first session Craig Wilson (Adolescent Trials Network) and Linda-Gail Bekker (Desmond Tutu HIV Centre) provided an overview of the current status of adolescents in HIV microbicide and vaccine trials, respectively. Dr Wilson outlined that because of differences in physical maturation (ectopy) and vaginal ecology it may be difficult to predict how adolescents will respond to microbicides without enrolling them. Also, there may be differences in douching and partner acceptability that may affect adolescent trials. He observed that it may not be necessary to enrol adolescents in phase III efficacy studies to get a product indication; that is, adolescents could be enrolled to get safety and acceptability bridging data. For example, if a product was found to be effective in adults if applied two hours prior to sex, an adolescent trial would assess if adolescents can observe this requirement. Meeting attendees heard that adolescents had been enrolled in microbicide trials (in South Africa, Uganda and Tanzania). Adolescent data and challenges have not been published to date.

Linda-Gail Bekker argued that adolescent enrolment in HIV vaccine trials is critical and mentioned that plans were underway to develop South African sites to host adolescent trials. Meeting attendees heard that there is little evidence to date that HIV vaccine safety may differ between adolescents and adults, but that it is likely that certain vaccines may be effective in adolescents when given at fewer or lower doses than adults. No HIV vaccine trial

anywhere in the world has enrolled adolescents, however, at the time of the meeting, plans were underway to enrol adolescents in HVTN 503 in South Africa should interim results from adult participants be promising; and there were plans to consider enrolment of older adolescents in PAVE 100¹.

In session two the ethical-legal challenges and concerns of adolescent participation in HIV vaccine and microbicide trials were reviewed. Quarraisha Abdool Karim (Centre for the AIDS Program of Research in South Africa) argued for the need to enrol adolescents because of their at-risk status, as well as the need to critically examine restrictive ethical guidelines and laws. Kolawole Oyediji (Nigerian HIV Vaccine and Microbicides Advocacy Group) argued that a particular advocacy focus on adolescents was warranted because of their at-risk status coupled with the resistance of many gatekeepers to address adolescent sexual issues. The session ended with Catherine Slack providing an overview thirty-one published articles on ethical-legal concerns in trials, clustered according to a popular framework (a comprehensive resource document is available on the GCM website).² She noted that there is little literature on adolescents in microbicide trials and few articles that compare ethical-legal complexities in both fields.

Session three was a rotational brainstorming session to identify problems common to both fields. Attendees from both HIV vaccine and microbicide fields identified the following shared concerns:

Collaborative partnership

- ❖ Ensuring stakeholder (especially community) understanding of the rationale for adolescent enrolment
- ❖ Overcoming the resistance and reluctance of key stakeholders like community groups and sponsors to test products in adolescents
- ❖ Ensuring more sophisticated community engagement
- ❖ Ensuring sound representation of adolescents for participation
- ❖ Ensuring good strategies for communicating with community groups and parents
- ❖ Sharing results with communities; and
- ❖ Ensuring a better understanding of cultural norms that may be impacted by adolescent enrolment

Scientific design issues

- ❖ Obtaining clarity on the timing and design of data collection from adolescents
- ❖ Getting data on adolescent sexual and risk behaviour to inform study design
- ❖ Developing clear correlates of safety and protection; and
- ❖ Managing discrepancies between age as an ethical-legal construct and age as a biological indicator of physiological maturity with respect to safety/ efficacy

¹ Subsequently, results from the HVTN 502 phase IIb HIV vaccine trial suggest that participants who were vaccinated may have increased risk of HIV infection, and this trial, plus the sister trial in South Africa (HVTN 503) have been stopped, and the field is processing the implications of these results for future products and protocols

² (see: [http://www.global-campaign.org/clientfiles/Essack,%20Slack%20&%20Strode%20\(2007\)%20Towards%20a%20roadmap%20summary%20of.doc](http://www.global-campaign.org/clientfiles/Essack,%20Slack%20&%20Strode%20(2007)%20Towards%20a%20roadmap%20summary%20of.doc))

Regulatory and ethical review

- ❖ Obtaining clarity on the regulatory framework for trials within a host country, including the data required for licensing and approval of products for adolescents within a host country
- ❖ Managing differences in regulatory requirements (e.g. for licensure) between countries
- ❖ Ensuring more clarity on the ethical-legal framework (e.g. consent requirements) in the host country
- ❖ Managing differences in ethical-legal frameworks across countries (e.g. risk-benefit categories for child research)
- ❖ Ensuring that the framework accommodates prevention research with children; and
- ❖ Ensuring that bodies involved in regulatory and ethics review have clear roles

Informed consent

- ❖ Clarifying consent issues like requirements for independent consent (age, emancipation); requirements for proxy consent (guardianship) and differences between consent and assent
- ❖ Balancing ethical-legal norms for age of consent with cultural norms; and
- ❖ Ensuring better tools to assess understanding

Risk-benefit ratio

- ❖ Managing risks associated with invasive procedures
- ❖ Offsetting potential social harms like stigma and increased risk behaviour (“behavioural disinhibition”)
- ❖ Heightening awareness of gender bias (e.g. girls may be more stigmatised)
- ❖ Managing the potential social harms associated with vaccine-induced false positive responses for HIV vaccine trials; and
- ❖ Ensuring good health services for adolescents

Ongoing respect for enrolled participants

- ❖ Protecting the confidentiality of adolescent volunteers; and
- ❖ Managing tensions between confidentiality requirements and legal norms to report certain disclosures (abuse, neglect, sexual offences like underage sex)

Attendees also noted that while there were important cross-cutting issues; there were a number of key differences between HIV vaccine and microbicide trials. For example, microbicide trials are more behaviourally complex, and rely on adherence to the product and accurate self-report unlike HIV vaccine trials where providers deliver the intervention. These included that for microbicide trials *consent* may be more complex as male sexual partners are also exposed to the product; *confidentiality* may be more complex because the product may be detected and *cultural preferences* around sex may be affected. For HIV vaccine trials: products may pose more *long term risks* (e.g. vaccine-induced antibody positive testing) however, ARV-based microbicides have the potential for resistance.

In session five an effort was made to understand the relative vulnerabilities of each field. Lori Heise (GCM) and Craig Wilson (Adolescent Trials Network) provided an overview of the microbicide and vaccine landscape respectively. It was noted that HIV vaccine trials enjoy more funding than microbicide trials (e.g. global vaccine funding is \$933 million while global microbicide funding is \$178 million) and more investment by pharmaceutical companies. At the time of the meeting, the microbicide field had to manage the negative publicity and

frustrated expectations associated with negative trial outcomes more so than the HIV vaccine field. Furthermore, at the time of the meeting, there was more debate for the microbicide field (than for HIV vaccines) around the assessment of safety, namely that the microbicide field does not enjoy clear measures of safety and that in the past an absence of reactogenicity (lesions, redness) has not necessarily correlated with product safety and reduced risk of HIV acquisition³.

In the last session, attendees were asked to identify key tools and resources that would be most impactful in order to move the adolescent agenda forward. Attendees identified the following resources; which would serve the agenda in both fields

- ❖ A clear accessible justification for adolescent enrolment (e.g. what is expected to differ for adolescents and adults in terms of safety and effectiveness for individual products)
- ❖ Clear accessible guidance on when and how to move products into adolescent trials
- ❖ Data on social harms from other youth trials setting out risk of stigma and increased risk behaviour; and
- ❖ Guidance on conducting ethical-legal audits in selected settings where trials may take place.

For the microbicide field, it was argued that a resource document on ARV-based products would be helpful. For the HIV vaccine trial field it was argued that a plan is needed on long-term access to confirmatory testing for vaccine-induced antibody responses.

The meeting was closed by Catherine Slack (HAVEG). She noted that the meeting achieved the goal of understanding common concerns in both fields, and identifying critical resources needed to accelerate the optimal involvement of adolescents in both HIV vaccine and microbicide trials. Both fields are working from the same premise that the enrolment of adolescents is critical and complicated. Despite common concerns, co-operation can be undermined by some organisational separation, ignorance of within-field issues and past conversations, and constrained resources. It is hoped that this meeting is one step in the direction of identifying common ground, and focussing finite energy on resources that can jointly serve both fields.

A “roadmap” will be developed shortly that further sets out the steps required for resource-development and identifies partners.

³ While debate at the meeting centred on safety assessment for microbicide trials and not for HIV vaccines, the subsequent results from the HVTN 502 phase IIb HIV vaccine trial suggest that assessing safety for HIV vaccines will be more complex than initially thought.

BOX 1 Recent developments: HVTN 502 and 503

On September 5th and 6th, 2007, the HIV/AIDS Vaccine Ethics Group (HAVEG), in collaboration with the Global Campaign for Microbicides (GCM), hosted a consultation on ethical and legal concerns associated with adolescent involvement in HIV vaccine and microbicide trials. The accompanying report briefly describes the discussions, findings and recommendations resulting from that exercise. Shortly thereafter, the HIV Vaccine Trials Network (HVTN), an international collaboration of scientists funded by the National Institute for Allergy and Infectious Diseases (NIAID) to test preventive HIV vaccines, announced the early closure of two trials of a prophylactic vaccine developed by the pharmaceutical company Merck. On September 21, 2007, the independent Data Safety Monitoring Board (DSMB) of the HVTN 502 “STEP” trial – a placebo-controlled phase IIb clinical trial involving 3000 high-risk participants in the United States, Canada, Peru, Brazil, Australia, Jamaica, Haiti, Puerto Rico and the Dominican Republic – recommended that the trial be discontinued because the study would not meet its efficacy endpoints as interim trial data showed no evidence of prophylactic or therapeutic efficacy. On October 23, 2007, in light of the STEP trial closure, HVTN also halted participant recruitment and vaccination for a second phase IIb clinical trial, called HVTN 503 “Phambili”, which had enrolled 801 at-risk participants in South Africa.

Unexpectedly, additional analyses of the STEP trial results suggest that volunteers randomized to receive the vaccine might have an increased susceptibility to acquiring HIV infection. There were 49 HIV infections reported in men who had received at least one dose of the vaccine, as compared with 33 infections in those who received placebo. Increased susceptibility appears more likely for those study participants who had high levels of pre-existing immunity to adenovirus type 5 (Ad5), used as the delivery vector for the gene fragments used in the Merck vaccine. In individuals with virtually no pre-existing immunity to Ad5 there were 20 infections in both the vaccine and placebo group. In the group with the lowest level of pre-existing immunity to Ad5, there were 8 infections in the vaccine group and 4 in placebo. In individuals with mid-range levels of pre-existing immunity there were 14 infections in the vaccine group and 7 in placebo. In volunteers with the highest level of pre-existing immunity to Ad5, there were 7 infections in the vaccine group and 2 in placebo. The figures above have to be considered cautiously because the trial was not designed to consider separate subgroups. Researchers still have yet to come up with a clear explanation of how, if at all, administration of the vaccine increased the risk of acquiring HIV. However, in the interest of safety, participants in both studies were told whether they received vaccine or placebo, and were encouraged to continue to return to the research study sites regularly for ongoing risk reduction counselling and HIV testing.

The closure of the STEP and Phambili trials affect the discussion and recommendations of the consultation in a number of ways. For example, it was reported at the meeting that plans were fairly advanced to submit protocols to regulatory and ethics committees to enrol 16 to 18 year-olds in HVTN 503/ Phambili. This is no longer the case. Furthermore, the discussion of the relative safety of HIV vaccines versus microbicides appears altered in the light of the STEP findings. At the meeting, it was noted by some participants that microbicide trials appeared to lack clear clinical or biological markers indicative of increased HIV infection risk. While trials of topical microbicides can look for evidence of reactogenicity like abnormal colposcopy findings,

increased bleeding, or other signs of genital tract inflammation, it was noted in the meeting that the absence of reactogenicity is not necessarily indicative of product safety, as the results of the Cellulose Sulfate trial suggested. While at the meeting some confidence was expressed that HIV vaccine trials enjoyed clear safety markers, the results of the STEP trial indicate a possible risk of increased HIV acquisition not unlike certain microbicide trials, suggesting that the issue of safety of HIV vaccines is more complex than initially supposed.

The urgent need for HIV prevention tools like microbicides and HIV vaccines has not changed, nor has the need for at-risk adolescents to have access to these products once they are commercially available. What has changed in light of the STEP and Phambili trial closures is the HIV vaccine field's assessment of the risks and benefits associated with participation. These recent events accentuate the need for transparent debate about adolescent involvement in prevention trials, which was begun at this meeting. It is our hope that the findings and recommendations of the consultation will provide some direction for the optimal involvement of adolescents in these important trials.

Welcome

(Lori Heise, GCM)

Lori Heise welcomed all participants. She remarked that HIV vaccine and microbicide stakeholders had been working in "silos" for years, and it was exciting to see both groups coming together to share their experiences. Ms Heise explained that this meeting originated in a consultation 4 years ago (published as "Re-thinking the ethical roadmap") which started to touch on adolescent enrolment in microbicide trials. She noted that young women will be the primary users and beneficiaries of microbicides but data is not being systematically collected about product safety and efficacy in ongoing trials. She briefly described the Global Campaign for Microbicides (GCM) as the civil society arm of the microbicide effort that aimed to both accelerate research and change how science is done; by forging a model of research with ethics and community at its centre. GCM originated out of the women's health movement that aimed to work on sexual and reproductive health for women. An example of a recent exercise undertaken by GCM is an assessment of the standard of prevention being offered to trial participants at various microbicide trial sites in Southern Africa.

Hoped for outcomes

(Catherine Slack, HAVEG)

Catherine Slack provided a brief overview of the origins of this meeting. The HIV AIDS Vaccines Ethics Group (HAVEG) was established in 2000 by the South African AIDS Vaccine Initiative (SAAVI) to research ethical-legal issues in HIV vaccine trials in South Africa. HAVEG and GCM met in late 2006 and an award was made in April 2007 to host a meeting between stakeholders in HIV vaccine and microbicide trials to debate adolescent enrolment and promote sharing across fields. Ms Slack outlined that a number of ethical-legal complexities associated with adolescent participation in HIV vaccine and microbicide trials exist. Many of these are related to the limited legal capacity of adolescents and the special protections present in most legal systems for persons under the age of 18. For example, a key complexity is the obtaining of consent: in many jurisdictions adolescents cannot consent independently to research and obtaining consent from their parents or guardians may be difficult as they may be members of child-headed households or living with a care-giver who is not a legal guardian. There have been many consultations and much written in the literature on the ethical-legal complexities. However, there has been limited analysis of the problems across

microbicide/ vaccine trials and developing/ developed country contexts, and limited identification of tools and resources that can be used to resolve these issues.

Ms Slack outlined the four desired outcomes of the workshop: (1) A better understanding of the key design and implementation issues that have emerged from the completed, current and planned adolescent vaccine and microbicide trials (2) A detailed analysis of the ethical-legal problems that face adolescent microbicide and HIV vaccine trials in the domains of community/ advocacy; ethics; legal/ regulatory; and science from a number of perspectives including uniqueness to microbicides or vaccines (3) Prioritization of these key ethical-legal issues, and (4) The identification of steps and resources needed to accelerate the optimal involvement of adolescents in these important trials.

2 ADOLESCENTS IN TRIALS

The objectives of the session were to review the status of adolescent involvement in HIV vaccine and microbicide trials by answering the following questions: Where have we been? Where are we now? Where are we going? What are the key problems and impasses that keep us from moving forward?

BOX 2 Who has enrolled adolescents or plans to?

Microbicide trials:

- ❖ Adolescents have been enrolled in microbicide trials in South Africa (Population Council, Carraguard) and Tanzania and Uganda (Indevus Pharmaceuticals, PRO 2000).
- ❖ Discussions are ongoing with sponsors to include youth down to 16 years old, where the ethical-legal framework permits. Once proof of concept is established in one of the ongoing trials; further planning for trials in adolescents could begin.

HIV vaccine trials:

- ❖ Adolescents have not been enrolled in HIV vaccine trials to date.
- ❖ If interim results had been promising adolescents may have been enrolled in South Africa (HIV Vaccine Trials Network 503) and in the United States (The Partnership for AIDS Vaccine Evaluation 100) however since the results of HVTN 502 were released (showing no efficacy and indicating the possibility of harm) these plans have been shelved. The HIV vaccine field is attempting to process the implications of these results for future products and protocols.

Adolescents in microbicide trials

Craig Wilson (ATN)

Craig Wilson described the work of the Adolescent Trials Network (ATN) whose primary mission is to conduct research, both independently and in collaboration with existing research networks, to explore promising behavioural, microbicial, prophylactic, therapeutic, and vaccine modalities in HIV-infected and HIV at-risk adolescents, age 12 through 24.

Dr Wilson provided an overview of microbicides. Microbicides attempt to act on either mucosal surfaces, tissue or cell surfaces, viral surfaces or inside cells. In mucosal surfaces, microbicides work through direct inactivation, preservation of acidic environment, enhancement/ restoration of commensal flora or by creating a physical barrier. In tissue or cell

surfaces, microbicides work through HIV cell receptors or co-receptors, or viral absorption or fusion. The mechanisms by which microbicides work on viral surfaces are through polyanionic polymers or envelope interacting agents and through anti-retrovirals inside of cells. Several general characteristics of desirable microbicides were outlined namely, microbicides should be potent against HIV and most other STIs, they should have preserved activity in the presence of seminal fluid, have no effect on integrity of mucosal surfaces or on commensal flora, they should preserve or enhance a low vaginal pH, be stable at tropical temperatures, compatible with latex, easy to use, have a low cost, and long shelf life and have good acceptability in terms of odour, colour, and taste.

He outlined that there are currently over sixty microbicide candidates in development; eleven in Phase I trials, one in Phase II/IIb, and three in Phase III. Some trials however have been stopped. Cellulose Sulfate (Ushercell), a polyanion with broad STI activity showed promising results in three Phase I and a Phase II trial; however, two Phase III trials were stopped in 2007 when the multi-country trial showed evidence of increased risk. The SAVVY trial was also closed - not due to safety concerns but rather as a result of lower than expected incidence rates.

The Nonoxynol (N-9) trial conducted with African and Thai sex workers resulted in N-9 users having higher HIV infection rates (14.7 versus 10.3 per 100 person years in the intervention versus control arm) and there was evidence of increased mucosal irritation. More recently, in the MIRA trial comparing condoms alone versus condoms plus diaphragm with readily available lubricant gel in South Africa and Zimbabwe (N= 5045, age 18-49, follow up planned for up to 24 months), analysis revealed an HIV incidence of 4.1% versus 3.9% per 100 woman years in the intervention versus control arm. Dr Wilson also discussed three active trials namely: (i) BufferGel versus PRO2000 0.5%: This is a phase IIb, randomized control trial with 3220 participants in 6 countries (Malawi, South Africa, Tanzania, USA, Zambia, Zimbabwe); (ii) PRO2000 0.5% versus 2.0%: This is a phase III, randomized control trial with 11,920 participants in 6 countries (Cameroon, S Africa, Tanzania, Uganda, Zambia, Swaziland) and (iii) Carraguard: a Phase III trial conducted at three sites in South Africa with 6270 participants (data collection for the Carraguard trial was completed in March 2007. See Population Council website for results: http://www.popcouncil.org/mediacenter/newsreleases/Carraguard_Findings.html). While there are multiple products in late phase trials, Dr Wilson emphasized that success is needed in at least one of the ongoing trials to demonstrate proof of concept. However, we will ultimately need multiple products which allow for extended daily use versus intermittent coitally-dependent use as well as products for rectal use.

Dr Wilson outlined that a number of biological issues may impact on adolescent trials, like vaginal ecology and physical maturation – called “ectopy”. It was noted that cervical ectopy decreases rapidly once sexual activity is initiated. Behavioural issues for adolescents like douching and partner acceptability will also impact on trials.

In terms of trial design, adolescent participation also raises a number of issues. In phase I/II studies there is relatively intense biomedical sampling which raises ethical concerns regarding the threshold of risks to which children will be exposed. Studies requiring sexually active adolescents raise a host of concerns, including whether adolescents below the age of consent to sex can be enrolled; and how to protect adolescent privacy needs around sexual risk data, sexually transmitted infection results etc.

He observed that it may not be necessary to enrol adolescents in phase III efficacy studies to get a product indication; that is, adolescents could be enrolled to get safety and acceptability bridging data. For example, if a product was found to be effective in adults if applied two hours prior to sex, an adolescent trial would assess if adolescents can observe this requirement.

BOX 3 Bridging studies with adolescents

Enrolling adolescents in efficacy trials may not be feasible because (i) some settings like the U.S will not have the thousands of high-risk adolescents required to have the statistical power to demonstrate efficacy and (ii) statutory rape laws that make sex below a certain age illegal prevent adolescents below that age (often younger adolescents) from enrolling in efficacy studies.

Nevertheless regulatory authorities require safety and immunogenicity data, at least, before a vaccine can be licensed for use by adolescents.

It may not be necessary to enrol adolescents in phase III efficacy studies in order to get a product indication; that is, adolescents could be enrolled in bridging studies instead.

Bridging studies allow researchers to extrapolate results from one population, formulation or dose regimen to another (Jaspan et al., 2008)⁴. Researchers get safety and efficacy data for adults and extrapolate this to adolescent age groups. However, bridging studies rely on correlates of immunity which are not yet available in HIV vaccinology (Bekker et al., 2005)⁵. Nevertheless, it may still be possible to conduct bridging studies in HIV vaccines by making use of good markers of protection.

A good example is the Human Papilloma Virus (HPV) vaccine trial. Phase III trials were done with 16-25 year olds. Researchers were able to work out that a particular marker (antibody to HPV) correlated, or was associated with, protection from HPV infection, allowing them to look for this marker in younger adolescents without requiring these younger adolescents to be enrolled in a trial with sexual activity requirements.

BOX 4 Major impedes for adolescent trials

- ❖ Difficulties in persuading investigators and networks that design large trials that adolescent enrolment is critical and feasible
- ❖ Complexities in engagement with regulatory authorities
- ❖ History of trials (e.g. the Nonoxyl-9; Cellulose Sulfate (CS) microbicide trials and now HVTN 502 and 503 HIV vaccine trials)
- ❖ The need to demonstrate “proof of concept” by a success in one of the ongoing trials

Adolescents in HIV vaccine trials (Linda-Gail Bekker, DTHC)

Linda-Gail Bekker (Desmond Tutu HIV Centre) presented an epidemiologic overview of the HIV/AIDS epidemic in terms of youth vulnerability; alluding to the UNAIDS model of considering generalised epidemics and target populations: there are presently 10 million youth

⁴ Jaspan et al. (2008). Inclusion of adolescents in preventive HIV vaccine trials: Public health policy and research design at a crossroads. *Journal of Acquired Immune deficiency Syndrome*, 47(1), 86-92

⁵ Bekker, L-G., Jaspan, H., McIntyre, J., Wood, R., Gray, G. (2005). Adolescents and HIV vaccine trials: What are the clinical trial site issues? *Journal of the International Association of Physicians in AIDS Care*, 4(4), 93-97

living with HIV, 63% of who live in Southern Africa. Youth in the Southern African generalised epidemic as well as Intravenous Drug Users (IVDU), Commercial Sex Workers (CSW), Men who have sex with men (MSM), and imprisoned youth worldwide have a much increased vulnerability to HIV. Licensure of a vaccine product requires that it be tested in the target population for both safety and efficacy; therefore adolescent populations need to be involved. In a recent study from the CARE group in Cape Town, published in *Vaccine*, it was shown that school-going adolescents were recommended as a target population for HIV vaccines. The data showing early debut and increased vulnerability in youth to HIV acquisition makes it necessary to utilise a small window of opportunity before sexual debut in the early teens for prevention interventions.

There are numerous obstacles to the development of a successful HIV vaccine. For example, there is no spontaneous recovery from infection despite vigorous immune responses and HIV also has antigenic diversity and hyper-variability. We currently lack a correlate of immunity which would allow bridging studies among population groups. In addition, other vaccines licensed for use in youth and children have shown us that responses may be different in adults and children. Often children are more immunologically responsive and smaller or less frequent dosing can be undertaken, e.g. HPV vaccine. There are thus scientific as well as regulatory reasons to have to test a vaccine in adolescents and preadolescents, as well as adults. The vaccine development process is a lengthy one and we need to ask when in the development path is it most appropriate to enrol adolescents and in which clinical trial phase. It was noted that the United States Food and Drug Administration (FDA) guidance on this issue could have been clearer, however, FDA concerns included (i) the need for a stepwise approach, "rolling down" from adults to older adolescents, and then younger adolescents (ii) the social impact, especially potential for increased risk behaviour and potential for a vaccine-induced antibody response (iii) the need for bridging studies (however the document (FDA, 2006) was not that clear on how to conduct bridging studies in the absence of correlates of immunity).

The scientific and epidemiologic data would support the involvement of adolescents in the clinical trial development process as a matter of urgency but many other issues also need to be considered and dealt with. There are many ethical, legal, socio-behavioural and clinical issues involved in enrolling adolescents in HIV vaccine trials. A major challenge for example, is that of adolescent care – countries may have clearly demarcated adult and paediatric care systems but adolescents may fall through the cracks. Prof Bekker suggested that before embarking on this work we need to build an environment conducive to adolescent enrolment. She used the Emanuel et al (2000, 2004) ethical framework of collaborative partnership, social value, scientific validity, fair subject selection, risk benefit ratio, informed consent, independent ethics review and respect for the study population to reflect on adolescent enrolment in HIV vaccine trials. She also presented some data to suggest that at least three vaccine sites in South Africa are well on the way to developing this conducive environment and a recent European and Developing Countries Clinical Trials Partnership (EDCTP) multi site grant awarded to DTHC would utilise preparatory research work to further enhance the environment in South Africa.

BOX 5 Adolescent; in PREP trials;

General proof of concept for PrEP or PreExposureProphylaxis comes from animal studies and Mother to Child Transmission studies with AntiRetroviral Therapy.

PrEP was previously not considered because of ART toxicities or unfavourable pharmacokinetics; however recent availability of ARTs with a longer half-life and lower toxicity profiles and the lack of success in other approaches have re-opened considerations of pre-exposure prophylaxis.

PrEP study designs require high risk populations with exposures to risk over a defined period of time. This includes young females in southern Africa, commercial sex workers, Intravenous Drug Users (IVDUs), and discordant couples. PrEP trials can use either daily/continuous or “coitally” dependent dosing and take the form of a single drug (Tenofovir) or a combination (Tenofovir/FTC, Truvada).

Active PrEP studies include:

- (i) Botswana (male and female, age 18–29, daily tenofovir, N = 1200);
- (ii) Multi-country eastern/southern Africa (female, age >18, daily tenofovir); India (men who have sex with men [MSM], age > 18, daily truvada);
- (iii) Multi-country (discordant couples, age >18, Truvada versus tenofovir); and
- (iv) Multi-country eastern/southern Africa (vaginal tenofovir versus PrEP).

Adolescents may be enrolled in PrEP trials sometime in the future. There are few biological issues in adolescent PrEP trials; however sexually active adolescents would need to be enrolled so statutory rape laws are relevant. In addition, screening procedures should not be too burdensome; and behavioural issues around product use will be important.

Discussion

Justification for adolescent enrolment: There needs to be a clear articulation (in a manner that advocates, communities and RECs will understand) of the evidence or “reasons for believing” that safety or efficacy for these products will be different in adolescents as opposed to adults. There was some debate about whether we should be advocating for adolescent enrolment in trials of all promising products or those with fewer potential social harms or less adherence problems.

Timing of adolescent enrolment: Participants argued that the timing of trials is a complex issue on which guidance is not clear. For example, it was not clear whether adolescents should be enrolled in a phase IIb study or a full-scale phase III. It was recommended that enrolling adolescents is an agenda that must be “pushed” with research ethics committees, regulators and community representatives. However, it was noted that there will be reluctance among regulatory bodies and sponsors to push ahead too quickly in younger adolescents given the recent trial results (e.g. Cellulose Sulfate). It was noted that there can be various outcomes of a phase IIb trial – if results are negative, nothing proceeds; if results are positive a phase IIb can “become” a phase III, or a phase III can be designed. Adolescent enrolment in a phase IIb

study would be justified on the grounds that “a product may work very well” and an important objective is to fast-track their enrolment.

Potential social risks: There were concerns that adolescents in trials might believe they are protected from HIV by the experimental product and therefore increase their risk behaviour, or fail to use known prevention options. This issue tends to be raised in all biological intervention trials. It was noted that generally in HIV prevention trials, risk behaviour as a whole tends to decrease while for a few individuals their risk behaviour may increase. It was suggested that data be obtained from other relevant studies with adolescents (e.g. Human Papilloma Virus [HPV] and Herpes Simplex Virus Type-2 [HSV2]) to assess the likelihood of this risk. The Population Council Carraguard trial collected data on risk behaviour in the previous month (but not on negative social impacts) and this data will be useful to inform this debate. It was noted that it may be very useful to develop common tools to assess sexual risk and social impact data that would allow comparison of data across trials. ATN has templates that they have developed to collect adolescent data across both vaccine and microbicide trials.

Potential biological risks: Participants pressed for more clarity regarding potential biological risks for adolescents in microbicide trials. For example, an earlier consultation (reported by Heise and Wood, 2003) identified that the cervix of adolescent girls may be less mature possibly placing them at increased risk of HIV infection for a period of time.

3 ETHICAL-LEGAL CONCERNS

The objectives of the session were to review the ethical-legal challenges, concerns and impasses in terms of adolescent enrolment.

Adolescents in trials: An ethical-legal analysis (Quarraisha Abdool Karim, CAPRISA, HPTN)

Quarraisha Abdool Karim (Centre for the AIDS Program of Research in South Africa) began with a presentation of epidemiological data on the national prevalence of HIV by sex and age in 2002; the age and gender distribution of HIV infection among 15–24 year olds in South Africa; specific HIV prevalence trends in women attending prenatal clinics in rural KwaZulu Natal; and the high HIV incidence rates by age in Durban & Vulindlela; all of which illustrated the high rate of HIV infection among South African youth.

She noted that enrolling minors in HIV prevention trials provides an opportunity to evaluate efficacy/effectiveness, assess acceptability, determine safety, and identify adherence issues. However, the context of research with minors needs to be considered. Presently there is caution and reluctance by Institutional Review Boards (IRBs)/ Research Ethics Committees (RECs), regulatory bodies, and scientists to enrol minors in biomedical prevention trials. Conflicting guidance in laws versus ethical guidelines is also a concern (e.g. in South Africa, national ethical guidelines allow for older adolescents to consent independently to research whereas the impending National Health Act mandates that parents/ guardians must consent for research).

Prof Abdool Karim described a number of ethical concerns of enrolling minors in trials. Adolescents are firstly a vulnerable population with regard to their level of experiential and physical maturity, their potentially diminished autonomy, and the legal and social challenges

they face. There are however more specific challenges related to HIV vaccine trials; these include the ability to adopt safer sex practices and the implications of an HIV-positive test result, such as the negative connotations, stigma and discrimination, violence and social ostracization.

She argued that requirements for parental consent to research might undermine efforts to respect adolescent rights to privacy (e.g. for their sexual risk information). She argued that moral judgments about sexuality make it unlikely that teenagers will seek parental permission for participation in HIV prevention research which would undermine efforts to recruit this much affected group into trials. She suggested that if parental consent is required, some adolescents will be prevented from participation (e.g. where there are no parents or guardians). She noted that the Council for International Organizations of Medical Sciences (2002) states that in some jurisdictions individuals who are below the general age of consent can be regarded as "emancipated" or "mature" minors and are authorized to consent without the agreement or even the awareness of their parents or guardians. For social-behavioural research like surveys of recreational drug use or child abuse, ethical review committees may waive parental permission if, for example, parental knowledge of the subject matter may place the adolescents at some risk of questioning or even intimidation by their parents. While arguing that parental consent may not be necessary or feasible for prevention research, Prof Abdool Karim acknowledged that adolescents may not make good decisions on their own - "this is the Achilles heel of adolescent prevention research".

Prof Abdool Karim argued that ethical guidance and laws, where restrictive or out of step with social realities, should be challenged. Prof Abdool Karim concluded that, notwithstanding underlying variability between regions, the vulnerability of youth is global. The HIV toll on youth globally and on adolescent women in particular makes it imperative to protect them from HIV infection. Social, political and economic drivers of risk and vulnerability need to be addressed. Several options for addressing challenges exist, including developing and evaluating effective models for collaborative and interdisciplinary approaches; supporting stakeholders to respond to emerging issues; and enhancing efforts at trust building, communication and fair benefits for research communities.

An advocacy perspective

(Kolawole Oyedeji, NHVMAG)

In his presentation Kolawole Oyedeji (Nigerian HIV Vaccine and Microbicides Advocacy Group) provided an advocacy perspective of adolescent participation in HIV prevention trials. Advocacy, according to Dr Oyedeji, can be defined as a systematic collective effort to influence the political environment, policy and research decisions, legislation, public perception, funding and community support for a particular issue, through a set of planned actions that are undertaken by a group of committed individuals or collaborating organizations. Advocacy creates the political will and momentum necessary to move the process of vaccine and microbicide development forward. Furthermore, advocacy sustains the needed pressure on the government to ensure that structures are put in place to facilitate prompt and wide access of people to successful products. Advocacy ensures accountability on the part of the scientific process to ensure that the public interest and the trial participants are protected. Advocacy helps to build capacity at grassroots to understand the science and ethics of vaccine development and research. Dr Oyedeji described four different types of advocacy: (i) Faith-based advocacy, which involves religious leaders and groups (ii) Community-based advocacy, involves parents and various other gatekeepers such as the media (iii) Peer education advocacy, which involves organizing workshops where discussions with informed peers can

take place; and (iv) Policy-makers advocacy, which advocates for legislative support and a conducive politico-administrative environment.

Dr Oyedeji then attempted to answer the question: Why focus on adolescents? (i) Adolescents are not well informed about sexuality, prevention of STIs and the consequences of unprotected sex or drug abuse (ii) The perceptions and opinions of many policy makers, public opinion leaders and gatekeepers are sometimes not supportive of sexual issues among adolescents, for example, they think adolescents will be more promiscuous if they learn about sexuality and prevention of HIV/AIDS (iii) Adolescents are severely affected by the HIV epidemic; globally 50% of all new HIV infections are in the 15-24 age group (UNAIDS,2006) so consideration must be given to enrolling this affected group (iv) Immune responses may differ in different age groups.

Dr Oyedeji described 4 operational strategies of advocacy that can be used in HIV prevention research (1) Public communication and enlightenment: Workshops, press articles, and public speaking engagements are used to direct campaigns at target groups like parents, peer educators, civic leaders, etc, to publicize the magnitude of the adolescent HIV epidemic, raise awareness of the need for adolescent HIV prevention research, and explain the potential risks (2) Policy advocacy: Key government functionaries and legal luminaries are engaged to clarify and strengthen existing laws and guidelines (3) Capacity building and empowerment: Community research literacy efforts, and consensus building is undertaken amongst key gatekeepers such as RECs on the kinds of protocols that could be considered ethically and legally sound with adolescent participants (4) National and international networking: Policymakers, media professionals, counsellors, peer educators, parents and religious leaders are engaged to gain support for trials.

Numerous challenges do however exist. Vaccine and microbicide trials, for example, involve the recruitment of healthy volunteers who may become infected during the course of the trial. Advocacy is needed to convince the community of the relevance of the trial. The age limit for informed consent may also create difficulty in adolescent enrolment e.g., adolescents may be reluctant to involve their parents or guardians in trials that monitor sexual behaviour. Opposition from various gatekeepers (such as parents, religious leaders, and media) requires careful planning to overcome. There are also challenges in terms of sponsor's commitments, for example, how long will the provision of post trial care last?

Dr Oyedeji described the lessons that can be learnt from NHVMAG which aims to promote public support for the participation of Nigeria in microbicide and vaccine research; mobilize active participation of Nigeria and her nationals in this research; and collaborate with other institutions and organizations locally and internationally for the rapid development of safe and effective HIV vaccines and microbicides for all.

Overview of the published literature (Catherine Slack, HAVEG)

Catherine Slack provided a brief overview of the published literature on adolescents in HIV prevention trials. Thirty one articles (see Appendix 2) were reviewed and summarised in terms of a logical framework (Emanuel et al, 2000; 2004). In terms of *community participation*, the literature identified as challenges: mistrust, especially among minority communities; misconceptions about trials and products; inadequate health-care infrastructure; cultural and religious norms; negative media coverage and poor awareness of rights. The recommendations made by the various authors were to engage with organisations that serve adolescents; educate potential participants, parents and community leaders; establish Community Advisory Boards (CABs) and involve them in protocol development; involve adolescents on

CABs; develop a comprehensive prevention and care infrastructure; co-ordinate/ align with existing youth prevention programs; and research relevant cultural and religious beliefs and taboos.

In terms of *social value*, many articles identify that adolescents are at high risk for HIV infection and young women, in particular, are at increased risk. Furthermore, major biological, hormonal, and physiological differences exist between adults and adolescents that make it difficult to predict responses to products without trials; e.g., vaccines may be most effective in adolescence and pre-adolescence (before sexual debut); and if adolescents are not enrolled, timely access to prevention products will be denied them. Recommendations include ensuring adolescent participation in order to provide data relevant to them; focusing on enrolment of young women to ensure products they can use; ensuring that funders (HVTN, International AIDS Vaccine Initiative (IAVI) develop plans for adolescent inclusion; ensuring that product developers incorporate adolescents into their plans; learning lessons from private sector experience with enrolling adolescents in trials of STI vaccines, e.g. Merck; GSK; and accelerating the study of promising candidates in adolescents with highest risk.

In terms of *scientific validity*, the literature points out that older adolescents present different requirements to younger adolescents; both biologically and legally. In contexts where sex below a certain age is illegal, adolescents below this age cannot be enrolled in efficacy studies where HIV infection is an endpoint. Recommendations have been made to enrol adolescents in trials when there is sufficient data from phase I and II studies in adults, without waiting for completion of adult efficacy studies; to use different trial designs for younger and older adolescents (e.g. to enrol older adolescents that can lawfully consent to sex in efficacy trials) and to initiate dialogue between sponsor/researchers and relevant National Regulatory Authorities (NRAs) prior to finalising design of efficacy or bridging studies.

In terms of *fair selection of participants*, many articles argue that adolescents are a vulnerable group because of their limited life experience and evolving cognitive capacity. Some adolescents have additional vulnerabilities, e.g. those who do not have legal guardians. Furthermore, identifying and retaining high-risk adolescents in trials is challenging and there is a lack of established cohorts of youth. There are also perceptions that youth are not at risk, by parents and youth themselves. It is recommended that the less vulnerable children (e.g. older) be enrolled first; that studies on HIV prevalence and incidence should be conducted; that sophisticated consent or assent processes be developed; that sites be customized for adolescents in terms of location, operating schedules (e.g. outside school hours), and staff practices (e.g. gender and youth sensitivity). It is also recommended that adolescents be involved as advisers on recruitment, education, and consent forms and that skills-building/ support groups to help youth adhere, are provided.

In terms of *favourable risk-benefit ratio*, the literature points out that the potential for adverse events need to be considered, as do risks associated with false-positive testing in HIV vaccine trials, risk of “therapeutic misconception” and increased risk behaviour (“behavioural disinhibition”). Other issues included sero-conversion or HIV infection; impact on school attendance and school work; the need to ensure fair payment to participants; and the need to consider appropriate benefits for adolescents. Recommendations were made to collect safety data and carefully evaluate adverse events; to collect data on social and biological risks to allow RECs to judge risks; to specify methods to identify and reduce harms in protocols; to address false positivity by differential testing; ID cards, a toll-free number, office for complaints, and education. Further recommendations were made to ensure referral for treatment, social support and disclosure to a trusted adult, if an adolescent becomes infected; to provide risk-reduction counselling tailored to the needs and sub-culture of adolescents; to debate models

for payment of adolescents and to ensure a range of care and prevention services are available.

Ethical and regulatory review issues include that NRAs require data from adolescents before licensing a vaccine for use in this age-group; that different NRAs may require different data before permitting adolescent enrolment and may have different concerns; that some NRAs have not issued guidance on the data they would require for enrolment or licensure. Other review issues include variation between and within countries on the requirements for child research; reluctance by RECs to enrol adolescents; limited reviewer capacity; complexities with ethical-legal concepts like “minimal risk” and additional review requirements in some countries. Recommendations have been made to undertake ethical-legal audits; lobby NRAs to issue guidance on their requirements; meet with NRAs to better understand their requirements; build REC capacity to review protocols; document data on risks for RECs; ensure adolescent or paediatric expertise on RECs; promote networking between RECs for a standardized approach; increase the acceptability of trials to local RECs; and ask international organizations like World Health Organization’s Institute for Vaccine Research (IVR) and HIV Vaccine Initiative (HVI) for advice and technical assistance.

Informed consent issues identified in the literature include variation between countries with regard to age of consent and the fact that within one country’s framework there may be poor harmonisation. Inadequate education; features of adolescent decision-making (like poor abstraction); and threats to voluntariness such as undue pressure from peers/ parents were also considered challenges. There were several issues surrounding parental consent such as whether parental consent was required/ important versus not feasible/ not ethically required; and whether/ how to accommodate adolescents with no guardians. Recommendations have been made to audit local laws and guidelines; consider transfer of guardianship if parents are not available or to consider if/ how other care-givers can be involved; design means to assess understanding of adolescents and parents; develop age-appropriate materials to promote understanding; increase contact time with counsellors and offset threats to voluntariness through advocates or cultural mediators.

In terms of *ongoing respect for enrolled participants*, the literature identifies challenges like adolescents’ privacy and confidentiality for risk information and test results; disclosures that trigger mandatory reporting responses; sexual disinhibition; and compensation for research-related injury. Recommendations include delineating adolescent rights to privacy and researching mandatory reporting requirements in the host country; explaining confidentiality, and its limits in consent forms and processes; training trial site staff to recognise and meet legal obligations; and implementing ongoing monitoring.

Ms Slack concluded that there is little published literature on adolescent microbicide trials. Similarly, little literature explicitly compares issues in both HIV vaccine and microbicide trials. In the summarized articles, most identified issues are relevant for both fields (except false positivity). There may be some differences between developed and developing countries in terms of comprehensiveness of the legal framework and capacity of stakeholders, or health-care infrastructure. In the summarized articles, few authors explicitly referred to tools, but many to success stories. Many commentators appeared to be arguing for the need to set national and international norms and standards for when adolescents should be enrolled and their protections.

Discussion

Major discussion items regarding ethical-legal issues in adolescent trials included:

Community participation: There is a need to target health-care workers for education about these trials. Furthermore adolescents themselves need special preparation; for example, adolescents may know a great deal about HIV and its transmission but not be able to apply that knowledge in a manner that protects them from HIV. Advocacy groups focussed on microbicide and vaccine work need to join forces for better co-ordination. HIV vaccine and microbicide trials need to occur in the context of broader prevention of HIV, so stakeholders must advocate for a broad spectrum of prevention services for youth. Adolescents who cannot be enrolled in actual studies can play valuable roles in the trial effort like educators, CAB members.

Preparatory work: While Willingness to Participate studies are important, their value must not be overestimated, given evidence that only approximately 10% of those indicating willingness actually enrol. Furthermore, maintaining cohorts of adolescents is very demanding and expensive.

Informed consent: The standard for parental consent for adolescent enrolment in clinical trials of experimental products is well-established in both ethical guidelines and previous consultations on adolescent enrolment in HIV vaccine trials therefore a deviation from parental consent is difficult to justify. However, poor harmonization of guidelines and laws around consent for child research has made it difficult for all stakeholders including activist groups to understand consent requirements.

Review: It was noted that various research ethics committees within the same country can apply different standards for parental consent for child research. It was also questioned whether the US FDA would licence a product trialled in a particular country if the ethical standards in that country differed from those in the United States. This was answered in the affirmative. It was observed that if investigators submit a protocol in the US for adolescent enrolment, it will require a specific scientific justification, especially given the relatively lower risk of HIV infection in US adolescents.

Benefits: Post-trial access to a successful product: It was observed that some National Regulatory Authorities take the issue of post-trial access seriously, for example, the South African Medicines Control Council recently did not approve an HIV prevention trial because the sponsor would not commit to provision of the product to participants post-trial if it was proven successful. It was also noted that a successful trial “gives one a piece of the puzzle” and does not inevitably lead to licensure and post-trial access for participants and the broader community. It was noted that microbicide trials are examining the issue of “introductory studies” that will enable participants to access the product while the time-lag for wider access is in effect.

BOX 6 *Access to treatment for HIV infection*

Some participants in both HIV vaccine and microbicide trials will become infected with HIV through on-going risk behaviour. Enabling access to treatment for HIV infected adolescents needs careful thought in both fields.

While some consensus has emerged on the need to ensure access to treatment, a major challenge for the prevention field is to identify and document various mechanisms to ensure access to treatment and care, which will be the subject of a future GCM consultation in 2008. Participants at the meeting questioned whether there is standardization in terms of access to treatment within and across the field of microbicides and vaccines, e.g. one participant noted that CS microbicide sponsors had funds available to ensure treatment which lead some community representatives to articulate that “some sponsors care more than others”. In response, it was noted that mechanisms to operationalise access to care vary between studies and sites, e.g. CONRAD and Population Council set aside money for care which is dispensed according to site needs and preferences, for example, by adding a clinician to the local clinic. A recent GCM assessment of care issues in microbicide trials (to be published later this year) revealed that while most trials had arrangements in place, these varied in terms of formality and degree of assistance provided to infected participants.

It was noted that in both fields some sponsors have articulated commitments to provide treatment should a national program not provide appropriate coverage, but in both fields these were “promises” that have not been tested yet. For example, HVTN has a policy that they will provide funding for ART for participants for a distinct period of time should they be unable to access ART in the public health-care system; as does IPM for microbicide participants. For NIH-funded researchers and trials, the investigator is responsible for addressing access issues and the NIH may favour environments where access to care mechanisms exist.

It was noted that late phase HIV vaccine trials are interested in the impact of the vaccine on disease progression (so called “secondary endpoints”) therefore there is interest in long-term monitoring of HIV-infected participants. In response, it was observed that with next-generation microbicides, protocols may assess how participants’ HIV infection progresses. It was noted that in some instances funding is just not available to ensure access to care e.g. one participant noted that microbicide trials are not backed by large Pharmaceutical companies. In response, it was argued that some HIV vaccines have been developed by small biotech companies, like Alphavax, that could not have afforded to provide access to care for infected participants.

It was argued that investigators must consider predictable care issues as part of the protocol, and build these into costs. It was also observed that apart from the narrow issue of access to ART, all trials have to consider the broader issue of how to “transition” participants to alternative forms of care after the trial when they have been receiving the bulk of their health-care in a trial setting.

4 POSITIONING MICROBICIDES & HIV VACCINES

Lori Heise provided an overview of the microbicide landscape. It is government, small bio-tech companies and academic networks who are presently developing products. There is no direct investment by big pharmaceutical companies. Research on microbicides began in the early 1990's with very little support or perceived scientific legitimacy. In the beginning it was mostly contraceptive researchers with little or no involvement of HIV scientists. The field struggled for many years to gain scientific credibility and funding. It is now firmly on the HIV prevention agenda but political support is weak and scepticism remains in some quarters (especially after recent concerns over the CS trial). Global vaccine funding is \$933 million while global microbicide funding is \$178 million. There is no investment by pharmaceutical companies in microbicides as there is no viable US or European market that is sufficiently lucrative to attract them. The Carraguard phase III trial was recently completed, and the results will be announced in December 2007 (see http://www.popcouncil.org/mediacenter/newsreleases/Carraguard_Findings.html for results). Two more trials will be complete in 2008/9 (but may not yield sufficient information to support licensure without more research – BufferGel; Pro 2000). No clear markers of safety or effectiveness are available to help guide decisions about which products to move forward. Ms Heise also outlined several challenges unique to microbicide trials. First, only women can be enrolled. This restricts where and how trials can be done. Pregnancy is an enormous problem in trials despite providing contraception and counselling and microbicide trials raise anxieties about women's empowerment, sexuality, etc. Second, it is harder to interpret results because one cannot "prove" whether the product was used correctly or not. The microbicide field has experienced several recent set backs. Several trials were stopped because incidence was not high enough. One trial was stopped because of a possible increase in risk (but the final result was not statistically significant). The N-9 experience left a bad taste in people's mouth even though N-9 was an existing spermicide never designed to stop HIV. Political support for microbicides is precarious at the moment because there is less government and scientific investment; concern is that people will give up in the face of set-backs. Ms Heise concluded that the field is shifting toward ARV-based microbicides which raises more complex and nuanced issues around safety.

Craig Wilson then provided an overview of HIV vaccines. There is a general familiarity with vaccines and there is much large scale use. Vaccines prevent disease not infection; however HIV vaccine developers are trying to develop a vaccine that prevents infection and disease. There has been much investment by pharmaceutical companies but many have recently dropped out as it is more profitable for pharmaceutical companies to fund treatments rather than vaccines. Initial vaccine research used the envelope of the virus to prevent infection but there has been a move to use the internal cell contents. There are ongoing attempts to improve vaccine delivery. He argued that HIV vaccine trial stakeholders to date are relatively confident that their safety measures are sound⁶. Even though novel techniques are being employed like DNA vaccines, some of these have been used in other trials like malaria vaccine trials. There are also numerous licensed vaccines that can provide information about ongoing safety. While vaccine researchers know how to evaluate vaccine safety, vaccine efficacy needs to be evaluated in full Phase IIB/III trials.

⁶ The trend towards increased susceptibility to infection among volunteers who received the vaccine in the HVTN 502 study has made the assessment of HIV vaccine safety more complex.

5 IDENTIFYING SHARED CONCERNS ACROSS FIELDS

This session took the form of a rotational brainstorming session. All participants were assigned to groups and to a station based on their primary field of expertise (Community, Science, Ethical and Legal / Regulatory). Each group addressed a standard set of questions at each station namely (a) What are the key issues? (b) What's unique to HIV vaccine trials versus Microbicide trials (c) What is unique to "South" or North" settings? (d) What are the priorities we should focus on? The primary group at each station had 45 minutes to discuss and answer the specified questions at their station. Each group then rotated to the next station and documented their agreement/disagreement with the previous group's inputs. The aim of this session was to allow everyone to discuss all the issues across all the themed areas.

The results are summarised here in a Table and narrative.

C = Community group

S = Science group

E = Ethics group

LR = Legal regulatory group

Shared concerns identified by attendees from both fields

Collaborative partnership

- ❖ Ensuring stakeholder (especially community) understanding of the rationale for adolescent enrolment
- ❖ Overcoming the resistance and reluctance of key stakeholders like community groups and sponsors to test products in adolescents
- ❖ Ensuring more sophisticated community engagement
- ❖ Ensuring sound representation of adolescents for participation
- ❖ Ensuring good strategies for communicating with community groups and parents
- ❖ Sharing results with communities; and
- ❖ Ensuring a better understanding of cultural norms that may be impacted by adolescent enrolment

Scientific design issues

- ❖ Ensuring more clarity on the timing and design of data collection from adolescents
- ❖ Getting data on adolescent sexual and risk behaviour to inform study design
- ❖ Developing clear correlates of safety and protection; and
- ❖ Managing discrepancies between age as an ethical-legal construct and biological distinctions relevant for safety/ efficacy

Regulatory and ethical review

- ❖ Ensuring more clarity on the regulatory framework for trials within host country, including the data required for licensing and approval of products for adolescents within a host country
- ❖ Managing differences in regulatory requirements (e.g. for licensure) between countries
- ❖ Ensuring more clarity on the ethical-legal framework (e.g. consent requirements) in the host country

- ❖ Managing differences in ethical-legal frameworks across countries (e.g. risk-benefit categories for child research)
- ❖ Ensuring that the framework accommodates prevention research with children; and
- ❖ Ensuring more clarified roles between bodies involved in regulation

Informed consent

- ❖ Clarifying consent issues like requirements for independent consent (age, emancipation); requirements for proxy consent (guardianship) and differences between consent and assent
- ❖ Balancing ethical-legal norms for age of consent with cultural norms; and
- ❖ Ensuring better tools to assess understanding

Risk-benefit ratio

- ❖ Managing risks associated with invasive procedures
- ❖ Offsetting potential social harms like stigma and increased risk behaviour (“behavioural disinhibition”)
- ❖ Ensuring awareness of gender bias (e.g. girls may be more stigmatised)
- ❖ Managing the potential social harms associated with vaccine-induced false positive responses for HIV vaccine trials; and
- ❖ Ensuring good health services for adolescents

Ongoing respect for enrolled participants

- ❖ Protecting the confidentiality of adolescent volunteers; and
- ❖ Managing tensions between confidentiality requirements and legal norms to report abuse (or disclose HIV status to an identifiable partner)

Table 1 Shared concerns identified by attendees from both fields

<i>Community</i>	<i>Science</i>	<i>Ethics</i>	<i>Legal/Regulatory</i>
Ensuring representation of adolescents on community structures	Ensuring community understanding of science and trials	Ensuring stakeholder understanding of the rationale for adolescent enrolment	Ensuring more clarity on the regulatory framework for trials (including roles) and that the framework accommodates prevention research with children

<i>Community</i>	<i>Science</i>	<i>Ethics</i>	<i>Legal/Regulatory</i>
Ensuring good strategies for communicating with community groups and parents	Ensuring better guidance about the timing and design of data collection from adolescents Ensuring better correlates of safety and protection	Ensuring more sophisticated community engagement	Ensuring better guidance about the data required for licensing and approval of products for adolescents; and timing of adolescent enrolment in trials
Offsetting social harms like stigma	Managing social harms like vaccine induced false positive responses and “behavioural disinhibition”	Offsetting social harms like HIV vaccine induced positivity and “behavioural disinhibition”	Managing tensions between confidentiality requirements and legal norms to report abuse (or disclose HIV status to an identifiable partner)
Protecting confidentiality of adolescent volunteers	Getting data on adolescent sexual and risk behaviour to inform study design	Managing risks associated with invasive procedures	Ensuring better tools to assess understanding
Balancing ethical-legal norms for age of consent with cultural concerns	Managing discrepancies between age as an ethical-legal construct and biological distinctions relevant for safety/efficacy	Clarifying consent requirements like age of consent to research	Clarifying consent requirements like guardianship; and differences between consent and assent
Ensuring good services for adolescents		Ensuring benefits for adolescents like health services	
Ensuring awareness of gender issues in adolescent enrolment	Sharing results with communities	Ensuring a better understanding of cultural norms that may be impacted by adolescent enrolment	
Overcoming resistance of key community groups to trials.	Addressing reluctance of sponsors and others to test products in adolescents	*****	****

Community	Science	Ethics	Legal/Regulatory
****	Managing differences in licensure requirements across countries	****	Managing differences in ethical-legal frameworks across countries (e.g. risk-benefit categories for child research)

Original contributions from the group-work (in a longer form) are presented below:

Community Group concerns

Representatives from the community group raised the following priority concerns:

- ❖ *Ensuring adolescent representation on CABs:* It was questioned whether adolescents should be included in adult CABs or whether youth CABs should be established. Communities may not be supportive of adolescent CABs, especially if a paternalistic attitude is present
- ❖ *Ensuring sound education and outreach:* Community interest is needed for successful trials. Communication and outreach strategies must be tailored to urban versus rural settings. It will be complex to explain the scientific, legal and ethical rationale for running adolescent trials and how to help communities to express their opinions. Two-way communication is critical, e.g. the ethical-legal framework must be explained to the community, but community input into policy changes is also needed. Adolescents will require general education with regard to sex, HIV, and clinical trials, and life skills training to assess the risks and benefits of taking part. They may need more help than adults in dealing with the consequences of trial participation. Trial messages to adolescents will be complex: on the one hand, they will be asked to have safe sex, but on the other hand sexual activity is required for efficacy trials. Site staff may struggle to talk to adolescents and parents about sex and HIV/AIDS, so mechanisms for communication need to be developed. In addition, adolescents may submit to adults in positions of authority, or resist them
- ❖ *Overcoming resistance:* Faith-based organizations (and others) may fear that adolescent involvement in trials encourages promiscuity. Policymakers may also be resistant to community demands to provide treatment for adolescents who seroconvert. Community adults may deny that HIV/AIDS in adolescents is a problem; as may adolescents themselves
- ❖ *Offsetting social harms, including stigma:* It was felt that there is likely to be more stigma for adolescents versus adults in general regarding sexual activity. Adolescents were also felt to have increased susceptibility to social harms given the presence of peer pressure, social cliques etc. Youth need to be empowered to be confident to stand up to peer pressure. It was felt that participation in microbicide trials may result in more stigma as a result of having to take applicators home and store them. It was also felt that stigma against entire communities involved in adolescent clinical trials by communities not involved or informed may be an important issue to address. It was

decided that the best way to reduce social harms and stigma was via community support

- ❖ *Managing confidentiality:* Parents might be friends with health care workers (in the context of trials attempting to recruit staff from local communities) which would make adolescents reluctant to attend their scheduled visits or be seen by certain staff members
- ❖ *Balancing consent with cultural respect:* The traditional age of consent may not coincide with that set out in the ethical-legal framework
- ❖ *Ensuring services for adolescents:* Services are needed such as prevention services, “ancillary care” or treatment for conditions identified in the study, including HIV infection and family planning, need to be in place before trials are started. Services also need to be available to adolescents who choose not to participate. Adolescent friendly staff who will not “parent” or judge adolescents are needed; and
- ❖ *Being aware of gender differences:* In communities, there is often a perceived gender difference in the age at which adolescents reach maturity. There is also often a “double standard” for boys and girls when it comes to sex. It is possible male involvement in prevention trials may have status value because of requirements for sexual activity. For females, this may lead to negative consequences.

Ethics group concerns

Representatives from the ethics group raised the following priority concerns:

- ❖ *Spelling out the justification for adolescent enrolment:* The need to enrol adolescents needs to be spelled out in accessible language in materials that can be used by a range of stakeholders
- ❖ *Clarifying consent requirements:* Many consent issues need to be clarified in the various jurisdictions where trials will take place, e.g. the age of independent consent, who should consent for child research and the extent of parental involvement required. It was argued that there is a risk of polarizing parents and adolescents when in reality the norm is some degree of interaction. It was felt that consent processes must be contextualized for each community where adolescents will be recruited, and that there should be greater input from the community into consent processes. It was argued that the consent process could not be administered in the same way that it is with adults. It was also felt that testing of comprehension needs to be more sophisticated, happen more consistently and that counsellors need to be better trained to assess understanding. It was also noted that ethics committees and regulatory bodies in some countries (like South Africa) have different standards for parental consent across HIV vaccine versus microbicide studies
- ❖ *Ensuring benefits and standard of care:* Adolescents should be offered a range of beneficial health services during participation. Guidelines are needed for managing

treatment care for HIV infection, VCT and pregnancy. Standards of care should be reasonably consistent across trials

- ❖ *Offsetting social harms:* Participants argued that long term access to confirmatory testing is critical for HIV vaccine trial participants. Such tests will be able to ascertain whether a participant is infected with HIV, or testing positive from vaccine-induced antibodies. It was argued that adolescents' may lack understanding of the experimental nature of the product. It was also felt that we need to address the potential for increased risk behaviour. Participants also observed that the strong perception from the public and key stakeholders that there is dishinbition in trials needs to be countered with actual data. It was argued that we need a better understanding of adolescents' 'sexual networking'
- ❖ *Understanding cultural issues:* These need to be better understood to ascertain if certain adolescent enrolment procedures would be insensitive in certain cultures
- ❖ *Managing risks associated with invasive procedures:* Participants observed that invasive procedures in trials like blood draws, or pelvic exams are another key issue. These procedures may have risks and cause concern for adolescents; and
- ❖ *Ensuring sound community participation:* It was stated that community participation for adolescent trials will have to be more sophisticated than adults. We need better awareness-raising, more educators, and espoused policies need to be better implemented. Staff may also need to be better matched to adolescent participants in terms of age. Adolescent friendly sites will need to be developed, for example sites that are open after school hours. This however raises additional complexities as, for example, samples cannot be processed after hours.

Legal and Regulatory group concerns

Representatives from the legal/ regulatory group raised the following priority concerns:

- ❖ *Clarifying consent requirements:* There is a lack of clarity in many legal systems about the age of independent consent for research; who can consent for children with no parents or guardians (e.g. wards of the state, in child-headed households); when children qualify as "emancipated" and who qualifies as a legal guardian. In addition, what steps should a researcher take to verify guardianship or parental status? The difference between consent and "assent" is not always fully understood. In addition, the age of consent for sexual activity (e.g. 16 in South Africa) may not correlate with social realities making "statutory rape" a common problem.
- ❖ *Clarifying requirements for the conduct and approval of adolescent trials:* There is ambiguous guidance about when adolescents should be enrolled (e.g. can adolescents be enrolled in trials at phase IIb or phase III?) and it is not clear what data is required for licensing and approval of products for adolescents. There may also be differences between requirements in developing and developed countries (which may delay development of products). Pharmaceutical companies may decide not to license drugs

in developing countries if they can't do so in developed countries. These requirements may not be clear to stakeholders, which may lead to disputes between bodies (ethics committees/IRBs, administrative agencies, courts). There may be some confusion about the roles of various bodies involved in regulation and it is complex for these different bodies to communicate with one another.

- ❖ *Managing different requirements in multi-national research:* Equity is complex when laws vary between countries. Specifically, the definition of adolescents may differ, as may the age of majority or age of consent to research, treatment or sex. Also approvable risks/benefit categories for child research may differ.
- ❖ *Working with inappropriate frameworks:* The regulatory framework may not be appropriate for scientific developments, e.g. prevention research does not fit neatly into the 4 categories for child research in the United States Code of Federal Regulations. In some restrictive frameworks, there are also insufficient exceptions to parental consent that will allow at risk children to access research.
- ❖ *Ensuring fair payment to child participants:* In some jurisdictions like South Africa, payment for trial participants has been governed by policies issued by the regulatory body (the Medicines Control Council).
- ❖ *Managing tensions between legal obligations of researchers to report versus respecting privacy:* Researchers must weigh adolescent right to privacy against laws requiring them to report (for example) abuse. Although the "best interests" standard can be used to consider how to weigh privacy against competing interests, it may be complex to apply across different groups. Another complex issue is whether health care workers are obliged to disclose HIV status to an identifiable sexual partner? It was noted that they may have a duty to encourage, counsel and facilitate disclosure with the participants' permission, but not be solely responsible for advising partners directly. There were concerns that in some settings exposing others to HIV may become a criminal offence, which will impact on health care workers. It was noted that in adolescent trials, a comprehensive consent document should outline what will and what will not be disclosed to parents. In the United States the use of a Certificate of Confidentiality is helpful.
- ❖ *Obtaining authentic understanding* from adolescents may be complex and procedures may need to be adapted for adolescent needs (a tool will be needed to assess understanding).

Science group concerns

Representatives from the science group raised the following priority concerns:

- ❖ *Ensuring better guidance on the timing and design of data collection from adolescents:* It was noted that there is ambiguous guidance around the timing of trials. The FDA guidelines seem to require safety and preliminary efficacy data from adults before

enrolling adolescents in HIV vaccine trials but expectations are not well-defined. This ambiguity may cause role-players to err on the side of delay and conflict with the goal to gather data on adolescents promptly. On the other hand, this ambiguity may be helpful given many options for collecting data, e.g. different ways of conducting bridging studies. There is a preference for using bridging studies if possible based on the regulatory principle to minimize the number of people exposed to risk. The problem is that it is difficult to determine what the most appropriate “bridging study” would be prior to having good human data

- ❖ *Understanding licensure requirements:* These may differ across countries depending on disease burden, and may affect whether sponsors seek licensure for adolescents as soon as possible (risk/benefit considerations are different). It is also difficult to know ahead of time what regulators are likely to find necessary/convincing. In South Africa, researchers can get advice from regulatory bodies, but they cannot get a formal pre-IND consultation where clear requirements are set out (like the FDA)
- ❖ *Developing clearer correlates of safety and protection:* It will be necessary to invest in research programs and consensus building to ensure this. *Age as an ethical/legal construct* is distinct from the relevant biological distinctions that may relate to safety or effectiveness
- ❖ *Addressing the lack of data on adolescent behaviour:* It was noted that better data is needed on sexual behaviour and risk to inform study design
- ❖ *Addressing stakeholder reluctance to test products in adolescents:* Typical concerns include liability, difficulty, and cultural sensitivity, and will need to be addressed
- ❖ *Sharing scientific data with communities:* Data has to be shared transparently and not “pre-packaged” in a manner that raises suspicions about transparency
- ❖ *Ensuring community understanding:* There was a particular concern about the degree to which participants and community members understand trials
- ❖ *Managing social harms:* For HIV vaccine trials, it is necessary to distinguish between real HIV and vaccine-induced seropositivity, and the need will persist after trials are over. One solution may be to reduce the costs of a more sensitive test or develop a new low cost way of establishing whether someone is actually infected with HIV (e.g. making PCR testing the standard for all health care interventions). A better understanding about how long vaccine-induced positivity lasts is also needed. There is a concern that adolescents might increase their risk behaviour if they think a vaccine or microbicide might be protective.

Attendees from both HIV vaccine and Microbicide fields were also asked to prioritise the concerns they listed. They prioritised the following:

Table 2 Priorities concerns ranked by attendees

Community	Science	Ethics	Legal Regulatory
Developing representative structures	Developing correlates of safety and protection	Clarifying consent requirements (e.g. age of consent)	Clarifying consent requirements (e.g. guardianship; emancipation)
Helping stakeholders understand rationale for adolescent enrolment	Helping stakeholders understand the best approaches for timing & design of data collection from adolescents	Helping stakeholders understand the rationale for adolescent enrolment	Helping stakeholders understand regulatory requirements, including timing
Addressing social harms like stigma	Getting information on adolescent sexual and risk behaviour to inform trial design	Addressing social harm of vaccine-induced positivity through long-term access to confirmatory tests	Helping stakeholders to understand and implement legal obligations to report disclosures
Addressing benefits like adolescent services	Helping stakeholders overcome reluctance to test products in adolescents	Addressing access to benefits like adolescent services	Addressing fair payment for adolescent participation

6 IDENTIFYING CROSS-FIELD DIFFERENCES

Meeting participants observed that representatives from the vaccine and microbicide fields were trying to talk across divides: “Some people know vaccines and not microbicides. Some people know science and not community”. Group-work participants were asked to consider similarities and differences between HIV vaccine and microbicide trials.

Identified similarities were that

- ❖ Both fields lack biological *correlates of protection*. Both fields do not have a good understanding of those features of the immune system that confer protection against HIV infection, that is, they both lack “correlates of immunity” or as one participant put it: “a tool that predicts efficacy”; and
- ❖ There is a lack of clarity about what *bridging* will look like, and how to “step down” from older to younger participants.

Outlined differences included the following:

1. For the HIV vaccine field, it was argued at the meeting that safety measures are better established for HIV vaccine trials than for the microbicide field. (However, subsequent

data from the HVTN 502 study indicates that safety for HIV vaccines is more complex than initially thought). It was argued that the microbicide field is collecting data on safety in as dedicated a manner as HIV vaccines

2. For microbicide trials, there is a special need to consider whether there are important *physiological differences* between adolescents and adults. There is no consensus on whether ectopy or differences in adolescent physiology may lead to differences in safety or effectiveness of microbicides
3. For microbicide trials, if adolescents are less *adherent* or their self reports of sexual behaviour are less accurate, it may affect study design (e.g., studies may need more power). This is less of a problem for vaccines because providers deliver the intervention
4. For microbicide trials, if there is an interaction between hormonal *contraceptive use* and risk of HIV acquisition, this may confound study results (e.g. what if Depo-Provera increases HIV infection risk?)
5. *A lack of information on sexual practices* may complicate trial design (e.g. adolescents may engage in more anal sex to avoid pregnancy). In microbicide trials specifically, a lack of information on cleansing practices may complicate trial interpretation
6. There will be a *broader target population* for HIV vaccines than microbicides (e.g. HIV vaccines could theoretically be provided to infants)
7. For microbicide trials, *menarche* could complicate the biological activity of the microbicide or its application
8. It was questioned whether safety or acceptability of microbicides would be different for *adolescent boys* undergoing circumcision during adolescence
9. *Consent* was felt to be more complex in microbicide trials as male sexual partners are also exposed to the product raising concerns around penile safety
10. *Confidentiality* of trial participation was also felt to be more complex in microbicide trials, because it is possible that male partners can detect when microbicides are being used
11. *Cultural practices* around sex may be especially impacted in microbicide trials because the product can alter sexual experience, e.g. in some settings dry sex may be preferred
12. It was argued that HIV vaccines may pose more *long term risks* (e.g. vaccine-induced antibody positive testing). However it was counter-argued that ARV-based microbicides have the potential to cause long-term harms, like resistance, although this latter risk is not well-understood
13. The issue of *product sharing* is also specific to microbicides, however it was believed that this could be countered with good education for adolescents

14. It was questioned whether there has been *inequity in REC decision making* between HIV vaccine and microbicide trials in terms of adolescent enrolment; and
15. *Risks related to vaccine-induced antibody positivity* are unique to HIV vaccine trials.

Identifying cross-setting differences:

Group-work participants were also asked to consider the impact of developed versus developing country settings for these trials. These were:

1. There may be *different trial phases* in developing countries (phase III) versus developed countries (phase I/II) due to different incidence rates
2. There may be fewer resources available in the developing world to treat adolescent participants for HIV infection and other conditions. This *differential access to health care services* may generate different obligations on the part of researchers. Healthcare infrastructure may be less adolescent-friendly in some parts of the world
3. *Consent* was also felt to be operationally more difficult in developing countries where many children may not have parents or guardians, and many adults work far from home. Variations regarding age of *consent* to research and treatment; emancipation etc is likely to vary between countries (and within). Social/cultural practices may be relevant, namely there may be more focus on involvement of the family in consent processes in developing countries
4. There may be *different risk-benefit ratios* for prevention trials between developed and developing countries. In developing countries there is generally a younger age of infection and subsequently more benefit to enrolling young people
5. *Review capacity* might be less in developing countries therefore training needs may be higher
6. There may be a less well-developed *framework of laws and guidelines* to protect adolescent trial participants in some developing countries than developed countries. E.g. in developing country settings, there are fewer formal, legally-binding processes for consultation with regulatory bodies (e.g., pre-IND consultation with the U.S. FDA). In Southern settings, it is possible that enforcement mechanisms for the law may be fewer
7. There may be differential reporting requirements and/or enforcement of reporting requirements between developed and developing country settings
8. *Licensure requirements* may be more stringent in developed countries with lower disease burden; and
9. For HIV vaccine trials, *background exposure* to the virus that comprises the vaccine vector (like Adenovirus 5 or BCG) will likely impact on vaccine responsiveness. In developing country settings like many in Southern Africa, there are higher rates of Ad 5

infection. Background rates of vaccination (e.g. with BCG) may impact on responsiveness and differ between countries (e.g. in South Africa adolescents have been vaccinated against BCG at birth).

7 RECOMMENDING NEEDED STEPS & RESOURCES

Participants were assigned to either and HIV vaccine group or a microbicide group. The objectives of the session were to identify the most impactful next steps for each field in terms of the enrolment of adolescents in trials.

BOX 7 What resources will move the agenda forward?

Attendees identified the following resources; which would serve the agenda in both fields

- ❖ A clear accessible justification for adolescent enrolment (e.g. what is expected to differ for adolescents and adults in terms of safety and effectiveness for individual products)
- ❖ Clear accessible guidance on when and how to move products into adolescent trials
- ❖ Data on social harms from other youth trials setting out risk of stigma and increased risk behaviour; and
- ❖ Guidance on conducting ethical-legal audits in selected settings where trials may take place.

For the microbicide field, it was argued that a resource document on ARV-based products would be helpful. For the HIV vaccine trial field it was argued that a plan on long-term access to confirmatory testing for vaccine-induced antibody responses is a much-needed resource.

HIV vaccine group recommendations

Representatives from the HIV vaccine trial sector set out the following recommendations:

1. *Develop a clear accessible resource* spelling out the scientific justification for enrolling adolescents that various stakeholders e.g. CABs can use. For example such a resource might spell out that there is no evidence for differences in HIV vaccine safety between adolescents and adults; however certain vaccines may be effective in adolescents when given at lower doses or fewer doses compared to adults (e.g., Hepatitis B)
2. *Find ways to mitigate the risks of vaccine-induced antibody response* in adolescents and to devise ways to reassure communities and IRBs about the risk of antibody response in adolescents. At present NIAID provides long-term access to confirmatory testing for participants. IAVI also does long-term follow-up, but it's not mandatory. SAAVI also has a plan in development. It was suggested that 1) an in-country procedure/ plan for long-term access be developed, as well as means to counter negative consequences from HIV testing for life insurance, applications to the army, and immigration. Such plans will require in-country, governmental support or WHO involvement or some central government office to ensure that after sites have been closed, people still have access to confirmatory testing; and 2) sharing of best practices
3. *Collect data on the risk of social harms (social impact)*, including changes in risk behaviour, stigma, job loss, impact on school attendance relevant to adolescent

participation. HVTN already has data on social impact. It reveals a trend towards younger participants reporting more events but this could be because adolescents share more information about their research participation not that they are more sensitive to social stigma

4. *Prepare for better consent methods to address adolescent-specific and cultural issues.* These include assessment of understanding. Existing resources could be adapted (HVTN 075 modified their consent form to develop an adolescent assent form that was much more adolescent-friendly; HPTN 035 has an open-ended assessment of understanding)
5. *Address legal requirements for mandatory reporting.* It was recommended that we refine further what needs reporting; and
6. *Increase community involvement* through education. It was suggested that innovative approaches to sharing information with communities be developed (e.g., the use of participatory, interactive methodologies). Better engagement between researchers and regulators is also needed

Microbicide group recommendations

Representatives from the microbicide sector set out the following recommendations:

1. *Develop a clear justification about the need to involve adolescents in microbicide trials.* Clarity should be gained about *whether safety and effectiveness will differ for adults and adolescents for individual microbicide products.* It was recommended that a panel of appropriate experts be convened to focus on this issue. It was recommended that all future trial protocols should explicitly address the inclusion or exclusion of adolescents, with a clear rationale and justification. It was also suggested that the Population Council (and others) who have already enrolled adolescents should review trial data with an eye to these issues. Researchers and sponsors should also be encouraged to study adolescent behaviour that may affect safety and efficacy issues (e.g., patterns of sexual behaviour, adherence, vaginal practices, etc.)
2. *Gain clarity about ethical and legal requirements for enrolling adolescents in clinical trials across different countries.* It was suggested that an ethical and legal review be conducted - of current ethical guidance and statutes relevant to adolescent enrolment in prevention trials. The goal is to develop a clear framework to help researchers developing protocols and committees reviewing protocols. It was also suggested that regulators and ethics committee members be invited to participate in on-going and future dialogue
3. *Aim to better understand special issues associated with the move towards ARV-based microbicides, and the impact on adolescents; and*
4. *Develop a decision framework to guide the field about when products should move into adolescent trials.* This will require dialogue with IRBs/RECs and other bodies about their needs, expectations, and ethical and legal requirements.

8 CONCLUSIONS & WAY FORWARD

The meeting was closed by Catherine Slack (HAVEG). She noted that the meeting achieved the goal of understanding common concerns in both fields, and identifying critical resources needed to accelerate the optimal involvement of adolescents in both HIV vaccine and microbicide trials. The meeting also helped stakeholders to begin to understand meaningful differences between the two fields impacting on scientific and ethical-legal concerns.

Both fields are working from a shared premise that the enrolment of adolescents is both critical and highly complex. They share common concerns around understanding and communicating the biological and behavioural differences that make adolescent enrolment critical and getting clarity on timing. In addition, both sets of stakeholders share the demand of working within unclear or inadequate frameworks for adolescent trials; and working with stakeholders that are reluctant to enrol adolescents in trials.

Despite common concerns, co-operation can be undermined by some organisational separation, ignorance of within-field issues and past conversations, and constrained resources.

This meeting aimed to take a step in the direction of identifying common ground, and focussing finite energy on the development of resources that can jointly serve both fields *including* user-friendly resources that will help stakeholders to understand the biological and behavioural differences that justify adolescent enrolment; the most appropriate timing in the sequence of trials for adolescent enrolment; and the ethical-legal and regulatory framework within which trials will take place. A “roadmap” will be developed shortly, that further sets out the steps required for resource-development and identifies partners.

Suggested citation:

Slack, C., Mamotte, N., & Essack, Z. (2008). *Ethical-legal concerns in adolescent microbicide and HIV vaccine research: Report on an international consultation*. Durban, South Africa, September 5-6, 2007. Global Campaign for Microbicides: 2008.

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Appendix 3: Agenda

Consultation on ethical-legal concerns in HIV vaccine and microbicide trials

Day 1 5 September 2007

0800 Registration

0900 Welcome (Lori Heise, GCM)

0910 Hoped for outcomes (Ann Strode, HAVEG)

Session I Checking on adolescents in HIV vaccine and microbicide trials; Where are we and why are we still here?

Objectives: Review the status of adolescent involvement in HIV vaccine and microbicide trials. Where have we been? Where are we now? Where are we going? What are the key problems and impasses that keep us from moving forward?

09:15 Adolescents in microbicide trials (Craig Wilson, ATN)

09:40 Adolescents in HIV vaccine trials (Linda-Gail Bekker, DTHC)

10:05 Questions and discussion

10:30 Tea

Session II Reviewing the ethical-legal problems in adolescent HIV vaccine and microbicide trials; What do we know? What new issues are coming up?

Objectives: Review the ethical-legal challenges, concerns and impasses. What issues have already been identified in the literature? What emerging issues are there?

11:00 Adolescents in trials: An ethical-legal analysis (Quarraisha Abdool Karim, CAPRISA, HPTN).

11:30 An advocacy perspective (Kola Oyedeji NHVMAG)

11:45 Overview of published literature (Catherine Slack, HAVEG)

12:15 Discussion

13:00 Lunch

Session III Refining the problems; A problem analysis

Objectives: Develop a more refined view of the problems in (i) Community (ii) Science (iii) Ethical and (iv) Legal / Regulatory domains. (a) What are the issues? (b) What are the priorities? (c) What's unique to HIV vaccine trials versus Microbicide trials (d) What is unique to "South" or "North" settings?

14:00 Group-work instructions (Vernon Solomon, HAVEG)

14:15 Group-work: Rotational brainstorming

16:30 Closing instructions

18:00 Cocktail and buffet dinner

Day 2 6 September 2007

Session IV Feedback from groups and toward consensus on priorities

Objectives: Discuss priorities identified by each group. Build consensus on most critical concerns

09:00 Feedback from groups

10:00 Facilitated discussion

10:30 Tea

Session V Positioning microbicides and HIV vaccines

Objectives: To identify where the fields are at in terms of history, science and political considerations

11:00 Input (Lori Heise, GCM)

11:10 Input (Craig Wilson, ATN)

11:20 Facilitated discussion

12:00 Groupwork (2 groups: HVT and MT considering most impactful next steps)

13:00 Lunch

14:00 Feedback from both groups

14:30 Activity mapping

15:00 Close (Catherine Slack, HAVEG)