Executive summary and recommendations from WHO/UNAIDS and AAVP consultation on: 'The inclusion of adolescents in HIV vaccine trials', 16–18 March 2006 in Gaborone, Botswana[a]

WHO/UNAIDS/AAVP International Expert Group[b]

This report summarizes the discussions and recommendations from a consultation held in Gaborone, Botswana (16–19 March 2006), organized by the joint World Health Organization (WHO)/United Nations Programme on HIV/AIDS (UNAIDS) HIV Vaccine Initiative (HVI) and the African AIDS Vaccine Programme (AAVP). The consultation considered key challenges and strategies in enrolling adolescents into HIV vaccine clinical trials, relevant to developing countries, in particular in eastern and southern Africa. Approaches were identified that might address and resolve country-specific challenges related to scientific, legal, ethical, regulatory and community aspects of the involvement of adolescents in HIV vaccine trials. This executive summary is formulated for a broader dissemination of the outcomes of the meeting to the general clinical, scientific and regulatory community involved in the review, approval and monitoring of clinical trials and potential licensing of HIV vaccine candidates. Four major topics were discussed and recommendations developed with regard to: (i) criteria for products selection and clinical trial design; (ii) ethical and legal issues; (iii) community acceptance and participation; and (iv) regulatory considerations. The recommendations of this meeting were further discussed and endorsed by the WHO/UNAIDS HIV Vaccine Advisory Committee.

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Objectives of the consultation

On 16–18 March 2006, the World Health Organization (WHO) and the African AIDS Vaccine Programme (AAVP) sponsored a technical consultation in Gaborone, Botswana, which brought together experts in scientific, clinical, ethical, regulatory and social aspects of HIV-1 vaccine research and development.

The key objectives of the consultation were to identify key challenges and strategies to enrolling adolescents into HIV vaccine clinical trials, in particular in eastern and southern Africa, discuss approaches for resolving country-specific issues and challenges, and formulate a strategy for broader dissemination of the outcomes of the meeting to the general research, clinical, ethics and regulatory community in the region.

Scope

The scope of this executive summary is to discuss key issues and strategies to address challenges for the inclusion of adolescents in HIV vaccine trials, and to provide recommendations for members of national regulatory authorities, members of ethics review committees, national policy decision makers and community representatives. The recommendations in this paper stem from the consultation in Gaborone, Botswana and a subsequent

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[a] This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the African AIDS Vaccine Programme (AAVP).

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WHO/UNAIDS HIV Vaccine Advisory Committee meeting held on 20–21 March 2006.

Definitions

Table 1 provides definitions of the various terms used throughout this paper.

Background

Epidemiology

The recent Joint United Nations Programme on HIV/AIDS (UNAIDS)/WHO AIDS Epidemic Update shows that despite improved access to care and treatment there were approximately 2.9 million deaths in 2006, of whom more than half a million were children. Of the 39.5 million people living with HIV in the world in 2006, 2.3 million were children under the age of 15 years. Almost half of the 4.3 million new HIV infections in 2006 were among young people (adolescents and young adults) 15–24 years of age, and half of those were among girls and young women. Approximately 77% of girls and women infected globally live in sub-Saharan Africa, where the major route of transmission is via unprotected heterosexual exposure [1–3]. Given the staggering scale of the epidemic in young people, a clear objective for any successful public health intervention to prevent HIV infection would be the vaccination of adolescents with an effective vaccine before they initiate sexual activity, at which time their risk of exposure to the virus increases dramatically.

For several sub-Saharan African countries for which HIV prevalence data are available, dramatic rises in HIV infection levels occur around the age at which sexual activity (whether consensual or forced) is initiated. This age (often between 15 and 17 years) varies by country or region, given differing cultural beliefs and practices. For example, in Mali and Ethiopia, almost 20% and 15% of girls, respectively, are married by the age of 15 years, whereas only 5% of girls are married by the same age in Malawi. In each country, the percentages of girls aged 15–19 years who reported having initiated sexual activity by the age of 15 years was the same or higher than the percentage of married girls by that age [1–3]. Given that the HIV epidemic in most parts of sub-Saharan Africa is no longer confined to core groups of individuals at higher risk of exposure to HIV, but involves large segments of the general population, the onset of sexual activity places adolescents at high risk of exposure to HIV. Protecting young people with an effective HIV vaccine before this happens would be a sound and cost-effective public health strategy. It is therefore imperative that as soon as a safe and effective HIV vaccine is developed, its licensure would occur simultaneously, both for adult and adolescent use.

Regulatory considerations

Preventive vaccines against serious infectious diseases are widely acknowledged to be among the safest and most effective interventions, with an enormous public health advantage. There is no reason to believe that HIV vaccine candidates with a potential to reduce the burden of disease will be any less safe than other vaccines, despite the fact that a number of HIV vaccine candidates are based on novel concepts that have not been used so far in any registered vaccine. Data from more than 85 HIV vaccine trials conducted to date demonstrate that all current vaccine candidates have excellent safety profiles [4].

Regulatory review and approval processes are designed to ensure the safety, efficacy and consistent quality of biological products, including future HIV vaccines. These processes must therefore be sufficiently robust, appropriately communicated and transparent to ensure public confidence and trust. The infrastructure and capacity to evaluate vaccines in general, and HIV vaccines in particular, may be insufficient in many developing countries, and even in some developed countries, to meet the high technical demands required for sound decision making. These demands, however, can and should be met. WHO is supporting collaborative programmes to assess the existing regulatory capacity for all vaccines in most developed and developing countries, and to identify existing gaps and needs for targeted activities focused on capacity strengthening of national regulatory authorities. In addition, through the WHO Initiative for Vaccine Research countries are provided with opportunities to receive independent expert advice on various aspects of HIV vaccine research and development, protocol design and clinical trials, including contentious policy issues, complex scientific and technical questions, and regulatory and ethical issues.

Medical regulatory decision making is based on balancing risks and benefits and should be evidence driven. There will thus be a need to collect data to support the licensure of HIV vaccines for use in adolescents during the clinical development of vaccine candidates. The risks and benefits will, however, vary based on regional HIV epidemiology, the specific product, local culturally relevant risk perceptions and other factors. Different regulatory frameworks may require different levels of detail in preclinical and clinical safety data in adults before the inclusion of adolescents in HIV vaccine clinical trials. Regulators and ethics committee members may also have differing views on potential safety concerns, e.g. some countries could place more weight on concerns regarding genetically modified organisms than others. All of these factors can play a role in the risk/benefit decision making by national regulatory authorities and ethics committees.

Clinical trial design

Several strategies for the inclusion of adolescents in HIV vaccine clinical trials were considered during the

Table 1. Definitions of some specific terms used in the position paper.

Term	Definition as used in the position paper
Adolescents	WHO defines adolescents as individuals between 10 and 19 years of age
Younger adolescents	Adolescents below the age at which an individual can legally have consensual sex: generally, this is below the age of 16 years, but will vary by jurisdiction
Older adolescents	Adolescents at or above the age at which an individual can legally have consensual sex: generally, this is the age of 16 years and above, but will vary by jurisdiction
Emancipated minor	Adolescents who have been given the rights of adults, e.g. to give informed consent for research, as established by national, provincial, state or local laws, e.g. a married adolescent, an adolescent girl who has given birth, an adolescent presenting for STI treatment. These definitions will vary by jurisdiction and not all localities would recognize the same emancipated minor status.
Informed consent	A process by which a subject voluntarily confirms willingness to participate in a clinical trial after having been informed of all aspects of the trial relevant to that decision and the documentation thereof. The elements to be conveyed to a potential research participant (e.g. the benefits of the research, the procedures and objectives, etc.), are defined by the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects and must be in accordance with the current revision of the Declaration of Helsinki as well as adhere to national legal requirements (e.g. the Code of Federal Regulations in the USA). The age at which this right to volunteer on one's own behalf differs by jurisdiction.
Assent	The right of a child to agree to participate in a clinical investigation. This must be accompanied by voluntary confirmation of an adult who has the right of informed consent or of parental permission for that child. Failure to object on the part of the child, absent affirmative agreement, may not be construed as assent.
Parental permission	Agreement of parent(s) or legal guardian for a child, who has also given assent, to participate in a clinical investigation. Parental permission must be obtained in accordance with the elements of informed consent.
Investigational new drug	A medicinal product, including pharmaceutical and biological agents, not yet approved for marketing, which is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. Clinical trials of investigational new drugs generally require authorization by relevant national regulatory authorities and ethical review committees, e.g. an institutional review board.
Efficacy trial	A large-scale (e.g. thousands to hundreds of thousands of volunteers) investigation, generally, double-blinded, randomized, and controlled, in human subjects, the primary objective of which is to determine whether the investigational new drug being tested provides a specified clinical benefit by furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. These studies are often referred to as clinical endpoint studies. Efficacy trials can include both pilot (see phase IIB TOC) and pivotal to licensure/registration (see phase III).
Bridging trial	An investigation in human subjects comparing ('bridging') two or more factors, e.g. manufacturing consistency lots, efficacy in different populations (e.g. younger adolescents to older adolescents to adults), launch lots to the efficacy lot. The bridge is based on a prospectively agreed-upon parameter, e.g. for vaccines, generally a validated immune correlate of protection. When no immune correlate of protection has been validated, one or more immunogenicity measures, as agreed upon between the clinical trial sponsor and national regulatory authority, may be used.
Phase I trial	A small investigation in human subjects (generally tens of people) of an investigational new drug, the objective of which is to gain preliminary safety, and sometimes, activity (e.g. immunogenicity) data. For vaccines, phase I trials are often conducted in healthy individuals at little or no risk of the disease the vaccine is intended to prevent. Phase I trials may be conducted in individuals at risk of the disease. Phase I trials may be blinded or open-label, with or without controls.
Phase II or IIA	A medium-sized investigation in human subjects (generally, hundreds of people) of an investigational new drug, the objective of which is to gain safety and activity (e.g. immunogenicity) data. Phase II or IIA trials of vaccines often do include individuals at risk of the disease. Phase II studies are generally blinded, randomized, and controlled.
Phase IIB TOC	An intermediate-sized investigation in human subjects (generally hundreds to thousands of people) of an investigational new drug, the objective of which is to gain pilot data on efficacy, as well as additional safety and activity (e.g. immunogenicity) data.
Phase III trials	Pivotal efficacy trials, bridging studies, large safety studies (intended to generate data on somewhat rare adverse events, i.e. those that would occur at a rate of 1/1000). Phase III studies are generally designed to provide pivotal data to support licensure/registration. Generally, involve thousands to tens of thousands of subjects.
Right to privacy/confidentiality	The basic human right of non-disclosure of personal identity and personal medical information. In some jurisdictions, there is a legal age at which this right is conveyed, e.g. the person permitted to give informed consent has the right to privacy/confidentiality, but the individual (child) for whom the consent/permission is being given may not have this right legally.
Vulnerable subjects	Individuals whose willingness to volunteer in a trial may be unduly influenced by an expectation, whether justified or not, of benefits associated with participation, or of retaliation in case of refusal to participate. Vulnerable subjects include children and those incapable of giving informed consent, among others, such as military personnel, prisoners, psychiatric patients, illiterate persons, etc.

CIOMS, Council for International Organizations of Medical Sciences; STI, Sexually transmitted infection; TOC, test-of-concept; WHO, World Health Organization.

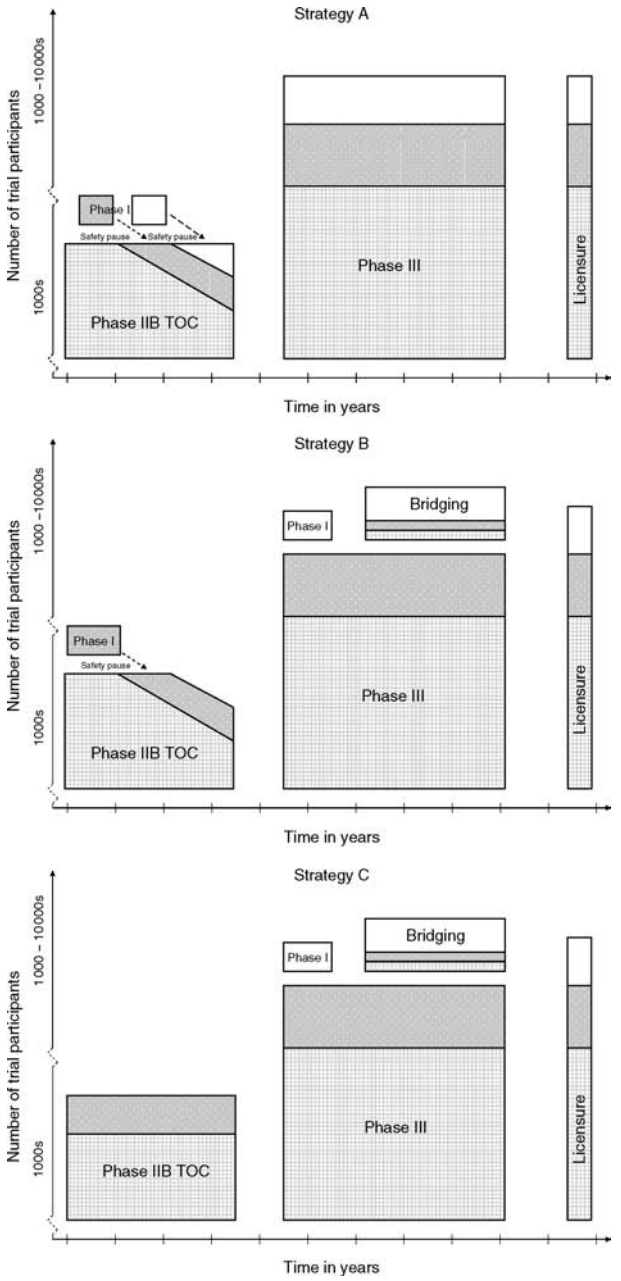

Fig. 1. Strategies discussed during the consultation for the inclusion of adolescents in HIV vaccine clinical trials[a]. Strategy A: When phase IIB test-of-concept (TOC) or III trial(s) begins in adults, phase I begins for adolescents, stepping down from older to younger adolescents with an integrated safety review pause. After successful completion of the phase I trial in adolescents, both older and younger adolescents could begin to be enrolled in ongoing phase IIB TOC or in a pivotal phase III trial. Strategy B: When phase IIB TOC or III trial(s) begins in adults, phase I begins for adolescents, stepping down from older to younger adolescents with an integrated safety review pause. Then older adolescents could begin to be enrolled in ongoing phase IIB TOC or in a pivotal phase III trial. A bridging trial would be conducted for younger adolescents in parallel to a phase III efficacy trial in adults and older adolescents. Strategy C: When phase IIB TOC or phase III trial(s) begins in adults, older adolescents would also be eligible for enrollment with a built-in safety pause to review initial safety data collected in adolescents (i.e. after a certain number of adolescents are enrolled and have received at least one inoculation). Phase I would begin for younger adolescents. A bridging trial would be conducted for younger adolescents in parallel with the pivotal efficacy trial. ☐ Younger adolescents; ▨ Older adolescents; ▦ Adults. [a]These scenarios are based on the assumption that the phase IIB TOC trials make an integral plan for the development of a particular HIV vaccine candidate and there may be situations in which phase IIB TOC trials will not be considered. In that case different scenarios may take place.

consultation. These strategies reflect alternative approaches to obtaining safety, immunogenicity and potential efficacy data in both older and younger adolescents. Biologically, legally and socially, these two age groups are likely to raise different data requirement issues and present different challenges. For example, when extensive safety and immunogenicity data in adults show sufficient promise to trigger advancement to efficacy trials in adults (18 years and older), there may be less need for additional safety and immunogenicity data in older adolescents (16–17 years old) before the initiation of efficacy trials in this population because the differences in physical status (weight, body mass index) and immune responses between older adolescents and younger adults are minor. With regard to younger adolescents (12–15 years old), however, the regulatory authorities and other decision makers may feel a greater need to verify safety and immunogenicity data by conducting additional phase I/II trials before proceeding to efficacy trials. Nevertheless, the experience with existing licensed vaccines does not indicate major differences in safety and immunogenicity profiles in younger adolescents compared with older age groups. On the contrary, some limited data presented at the meeting suggested that younger age groups may be better responders to vaccination.

Equally important from a legal point of view is that in some countries it may not be possible to enrol younger adolescents in efficacy trials in which, on the one hand, sexual activity serves as an eligibility criterion, whereas on the other the existing laws may classify sexual activity in this age group as 'statutory rape'. In these settings, the inclusion of sexually active younger adolescents might imply that investigators and consenting parents or guardians support an illegal activity, which would be considered unacceptable. Therefore, the trial design scenarios discussed below distinguish between older and younger adolescents, using various combinations of phase IIB test-of-concept (TOC) and pivotal phase III trials. Each of these strategies may have advantages and could be considered by the national regulatory authorities and ethics committees. Three different strategies for the involvement of adolescents in HIV vaccine trials are depicted graphically in Fig. 1.

In Strategy A, parallel to phase IIB TOC or phase III trials in adults, a separate phase I trial would be conducted for older and younger adolescents, starting with older adolescents and stepping down to younger adolescents, with an interim review of safety and immunogenicity data between enrolment of each of the two age groups. In the case of positive results, both older and younger adolescents could be enrolled in the ongoing phase IIB TOC or phase III adult efficacy trial(s). This approach may be appropriate when there are reasons to anticipate less favourable results in adolescents than in adults or when there is limited experience with a certain vaccine candidate among young adults 18–24 years old. This strategy could eliminate the need to conduct additional so-called 'bridging trials' in order to confirm the relevance of results obtained in adults to the adolescent age groups, including younger adolescents.

Strategy B could be applied when testing an HIV vaccine candidate for which significant safety and immunogenicity data are available in adults, including younger adults (18–24 years old). Furthermore, this strategy could be applied in situations in which legal constraints regarding statutory rape may exist for the enrolment of sexually active younger adolescents. In this scenario, in parallel with a phase IIB TOC trial or phase III trial(s) in adults, a phase I trial would begin for older adolescents and step down to younger ones, with a safety pause integrated between the two age groups, as in the earlier scenario. Older adolescents could then be enrolled along with adults in an on-going phase IIB TOC or phase III efficacy trial. For younger adolescents, a bridging (safety and immunogenicity) trial would be conducted later in parallel to the pivotal phase III trial among adults and older adolescents.

Strategy C would apply when testing an HIV vaccine candidate for which significant safety and immunogenicity data are available in adults, including younger adults (18–24 years old), and would also apply in situations in which legal constraints regarding statutory rape may exist for the enrolment of sexually active younger adolescents. With this strategy, older adolescents (16–17 years olds) would be enrolled in a phase IIB TOC or efficacy trial along with adults based on the existent safety and immunogenicity data in younger adults. For younger adolescents, a phase I safety and immunogenicity trial followed by a larger bridging trial would be conducted in parallel to the pivotal phase III trial in adults and older adolescents. Whereas the bridging trial could collect data on the incidence of HIV infections, should they occur, sexual activity and risk of HIV would not be a requirement for enrolment.

Vaccine candidates

The current product pipeline was reviewed during the consultation, as well as in a number of the latest publications [5–8]. The consultation considered vaccine candidates that are more likely to be proposed for trials involving adolescents. Various HIV vaccine strategies are being developed in parallel, some of which may have certain indications or limitations for their use across all ages, whereas others may be specifically targeted at specific age groups. Some vaccine candidates at the forefront of development, such as recombinant proteins or DNA-based vaccines, were thought to have a greater potential for application for all ages, because the phenomenon of preexisting vector immunity is not relevant for these strategies. On the other hand, the application of live vectored vaccines would have to consider possible interference as a result of preexisting immunity to the vector. The prevalence of preexisting antivector immunity in children and adolescents could be significantly lower compared with adult populations, which would make this type of vaccine more suitable for use in children and adolescents than adults. Strategies could, however, be applied to overcome this barrier, such as the use of non-replicating or other specially selected vectors not commonly found in humans. Examples of other vector systems in development, which may be better targeted for infants, include those based on bacillus Calmette–Guérin and measles vaccines, which are commonly used in ongoing universal immunization programmes. Of note is the fact that the immunogenicity of measles virus-vectored vaccines in measles-immune populations is currently unknown. The consultation emphasized the importance of promoting the development of HIV vaccines that would be suitable for use in both adult and adolescent populations.

Ethics and legal frameworks

Children and adolescents represent vulnerable individuals who must be afforded special protections [8]. At the same time, epidemiological data show that sexually active adolescents are especially affected by the HIV epidemic, both biologically and behaviourally. As with all medical regulatory decision making, risks should be weighed against potential benefits for specific target populations. Clinical research involving healthy minors should thus be considered and balanced against the moral obligation to protect adolescents from disease, if possible through vaccination. Therefore, consideration should be given to the consequences of overly protective laws and regulations that limit the participation in HIV vaccine-related research and clinical trials of those groups who are precisely more likely to benefit from a successful HIV vaccine.

In addition to the ethical principles outlined in the Declaration of Helsinki and the UNAIDS guidance document on 'ethical considerations in HIV/AIDS preventive vaccine research', this paper also considers existing provincial/state and national laws and legal frameworks [9,10]. The participants in the consultation acknowledged the presence of important differences and variations with regard to existing local laws and

regulations that specify definitions directly relevant to the participation of adolescents in HIV vaccine trials, such as definitions of the age of majority, the age of consent for research, the age of consensual sex, as well as the meaning of emancipated minor status. In addition, participants recognized that other locally relevant cultural and religious beliefs and practices must be considered when determining the acceptability of clinical research involving adolescents.

Whereas this position paper pays special attention to the needs and requirements for the inclusion of adolescents in HIV vaccine trials, it should be noted that participants did not consider HIV vaccines or the inclusion of adolescents in HIV vaccine clinical trials as exceptional in their requirements. Experience, and the precedents set with the development of other vaccines for adolescent use, such as human papillomavirus vaccines, one of which has recently been licensed, and ongoing trials of a candidate herpes simplex type 2 vaccine, were extensively referred to during discussions on strategy development.

Recommendations

Clinical trial design

For products that would have an indication for use in both adolescents and adults, it is imperative that there be no delays in achieving simultaneous licensure/registration for both populations. It is therefore recommended that adolescents be included in HIV vaccine trials as soon as possible when a candidate has sufficient promise to advance into a phase IIB TOC or phase III efficacy trial in adults.

The criteria to support the inclusion of adolescents in HIV vaccine trials would include consideration of all available safety and immunogenicity data generated in preclinical studies, phase I/II clinical trials in adults, preliminary assessment of potential social harms related to the participation of both adults and adolescents in HIV vaccine trials, and other relevant information required for an in-depth risk–benefit analysis, e.g. the HIV epidemiology in the area of the clinical trial site, etc. It is therefore recommended that data on social harms (e.g. therapeutic misconception, risk compensation, discrimination as a result of vaccine-induced seropositivity, etc.) be collected during specially designed sociobehavioural studies and clinical trials involving adolescents. These data should be carefully analysed and made available on a regional basis to be considered in the planning, design and implementation of other trials elsewhere in the region. In addition, as with clinical trials in adults, data on clinical risks (potential product-related adverse events) should be carefully collected in all phases of vaccine trials enrolling younger adults and adolescents.

As a result of physiological differences associated with age, immune responsiveness tends to decrease with increasing age. In addition, sex hormone profiles undergo dramatic changes during the puberty period, which can affect immune responsiveness [11–13]. Furthermore, physiological changes start occurring in the female genital tract mucosa, a portal of entry for HIV during sexual transmission, which may differentially affect the risk of infection upon exposure, and thus vaccine efficacy. Reactogenicity profiles of a product may also change with increased immune responsiveness. For these reasons, among others, it was suggested that for each product the dose, volume, and administration schedule may need to be further fine-tuned specifically for younger adolescents from what is shown to be optimal in adults.

In certain situations, it may be especially challenging to include younger adolescents in trials using HIV infection as a primary endpoint. HIV prevalence in younger adolescents is relatively low (increasing with age), suggesting a low incidence until the age of approximately 14–16 years, depending on the region. Also, as mentioned previously, there may be significant legal and ethical barriers to the enrolment of younger adolescents into a clinical trial in which sexual activity is directly linked to achieving primary endpoints. In full recognition of these challenges and the lack of identified correlates of immune protection against HIV, it is recommended that strategies based on the use of bridging studies designed for safety and immunogenicity testing but not including HIV infection as a primary endpoint be considered as an alternative for younger adolescents. In such studies HIV infection could be included as a secondary or exploratory endpoint. The most appropriate type and design of such bridging strategies will need to be determined on the basis of early and detailed communication between trial sponsors/investigators and national regulatory authorities.

It is further recommended that the design of these bridging studies in younger adolescents parallel efficacy trial(s) being conducted in adults and older adolescents to facilitate comparison and bridging the results of these trials. This strategy would also facilitate the generation of efficacy endpoint data (e.g. HIV infection, viral load and CD4 cell counts in younger trial participants who acquire HIV infection during the trial) should such efficacy endpoints occur. These data could be analysed for statistical trends, even though the bridging trial would not be powered to demonstrate efficacy nor would it be a primary objective of the bridging trial, thus obviating the requirement for inclusion criteria to support the collection of such efficacy data.

Finally, it will be important that the clinical protocol, informed consent documents and process, as well as communications with the broader community avoid identifying efficacy trial participants as being 'high-risk' individuals, given the resulting stigma that could then potentially be associated with trial participation.

Especially in areas with generalized epidemics, where the majority of the general population is at risk of HIV infection, the term 'high risk' may not be particularly meaningful for designing vaccine trials.

Regulatory considerations

Trial sponsors and investigators should initiate dialogue with national regulatory authorities early before the final design of efficacy and bridging trials. Topics for this dialogue would include the data that the national regulatory authorities consider necessary to support licensure/registration in adolescents, the parameters that would be the basis for bridging, and the data that are needed to initiate trials that include adolescents. Furthermore, consideration should be given to designing and conducting trials in a manner that collects data needed for regulatory decision making, including, but not limited to, safety data on both social harms and clinical risks.

For those national regulatory authorities or ethical review committees that lack experience in HIV vaccine trials or in adolescent research, the advice and assistance of WHO and UNAIDS could be sought. WHO has established a forum for regulators in the sub-Saharan African region to meet periodically and to discuss regulatory issues of common interest. More information on this forum may be found at: http://www.who.int/immunization_standards/vaccine_regulation/africa_network/en/index.html. Several HIV vaccine-specific training workshops for Institutional Review Board members have been conducted by the WHO AAVP Working Group on Ethics, Law and Human Rights, and the capacity needs of institutional review boards have been formally evaluated [14]. In addition, efforts are ongoing to establish a regional pool of HIV vaccine experts to further encourage regional collaboration and capacity building. Training through the use of case scenarios may strengthen understanding and facilitate decision making.

With regard to the present state of knowledge, the usefulness of animal models to assess the safety and efficacy of HIV vaccine candidates remains unclear, and correlation with the human situation is not completely understood. Although safety studies in animals are generally essential for the drug and vaccine regulatory processes, it would not be appropriate for the existing animal models for HIV to present a regulatory hurdle to vaccine developers. The safety of vaccine products in an unscreened population for which a successful HIV vaccine would ultimately be used, including potentially HIV-infected individuals, would need to be established in human clinical trials (for common adverse experiences) and during postmarketing surveillance (for rare events).

Ethical and legal issues

It is imperative that HIV vaccine trials be conducted in a manner that ensures the protection of human rights and sex equality. Trials must also be conducted in compliance with the laws and regulations applicable at the trial sites, including those related to the legal age of consent, the age of majority, the legal age for consensual sex, and other aspects that may have an impact on the conduct of HIV vaccine trials. Therefore, undertaking a survey of the applicable local laws is an essential requirement to ensure required compliance before making plans for such trials in a particular country.

As with all other trials involving adolescents, HIV vaccine trials involving adolescents will require the permission of a parent(s) or legal guardian, along with the assent of the adolescent. Furthermore, adolescents are entitled to confidentiality of information disclosed or discovered in the recruitment process and during the conduct of the trial. There may be specific exceptions to this for legal or ethical reasons, but those exceptions should be prospectively identified for the adolescent during the informed consent process.

During recruitment, adolescents may be approached initially in various settings (e.g. clinics for the treatment of sexually transmitted infections, voluntary counselling clinics, family planning programmes). To protect the adolescent's confidentiality, however, workers in the clinic or programme setting where recruitment is taking place should first ask the adolescent whether they would be willing to speak to a researcher. Investigators should ask those adolescents being recruited for endpoint efficacy trials whether their parents are aware of their sexual behaviour, and explain to them that if they do not have the legal right to autonomous consent, then parental permission will be required for enrolment. Exceptions to the need for parental permission may occur in the case of emancipated minors, consistent with state/provincial or national laws.

During the informed consent process, it is recommended that investigators conduct the consent (parental permission) and assent processes separately with the parent(s) and adolescent(s), respectively. This strategy would ensure confidential counselling for the adolescent, and protect the adolescent's privacy. It will also be important to determine that the adolescent understands what s/he is assenting to (e.g. purpose, procedures, risks, benefits, inconveniences, confidentiality protections and any limitations, duration of participation, right to withdraw at any time). Informed consent is a process that continues throughout the trial and involves ongoing dialogue among researchers, parents and adolescents. The consent process and document should describe what information regarding the adolescent will or will not be disclosed to the parent(s) or legal guardian, as well as what medical or other services will be provided to the adolescent, as needed, without further parental permission.

In some settings, children may have guardians who have not been legally recognized by a court as such.

Adolescents who do not have parents or legally recognized guardians should not be automatically excluded from participation in an HIV vaccine trial. Participation could be considered for such adolescents who wish to participate in a trial, as long as a mechanism can be established in compliance with the local laws and legislation, as well as with national regulatory and ethical requirements. In addition, mechanisms should be established for an independent evaluation, by an individual with appropriate skills, of the capacity of such adolescents to give informed consent. It will not be possible to enrol all adolescents in HIV vaccine trials, including those who have the most potential to benefit, given that their heightened risk of HIV infection may be a result of heightened vulnerability, such as being homeless, orphaned, abused, etc.

HIV vaccine research must be conducted in the full acknowledgement that difficult issues will be faced, including the occurrence of HIV infections, social harms and the special needs of adolescents, etc. Consideration should be given to such issues in the design of the study. During the conduct of the trial, sponsors and investigators should establish procedures to provide support for adolescents who become infected with HIV, including treatment referral, care, social support and assistance in disclosing their status to a parent(s) or guardian. Exceptions to the disclosure of an adolescent's HIV infection to parent(s) include cases in which such disclosure would be against the best interests of the adolescent, to be determined by the investigators in consultation with the adolescent. Furthermore, information on social harms should be systematically gathered throughout the trial and steps taken to prevent or redress any such harms.

Sponsors and investigators should make provision for the treatment of vaccine-related adverse events that may occur during the trial. Even after completion of the trial, sponsors and investigators should establish procedures for providing ongoing support for potential trial-related social harms, including the need for support in cases of vaccine-induced seropositivity (individuals who are not infected but would test positive by a standard HIV test as a result of the intended vaccine-induced immune response).

Community acceptance and participation

An important consideration for trials involving adolescents is the establishment of adolescent-friendly trial sites. All trial site personnel, including drivers, receptionists, recruiters, counsellors, physicians, nurses, etc. should be trained in both adolescent and sex sensitivity to foster a non-judgemental and supportive environment. To facilitate the development of an adolescent-friendly environment, consideration should be given to the possible extent of employing adolescents to carry out defined clinical trial activities, such as acting as peer counsellors, receptionists or greeters, as well as including adolescents in advisory groups.

Transparent communication is the key to success in establishing trust and accountability. Plans should be made for information sharing, education, and advocacy for community leadership at all levels (local and national) and for communication with news media. Placing planned HIV vaccine trials in the context of other precedents (other trials that have included adolescents) may help normalize communications through showing that HIV vaccine trials involving adolescents are not exceptional.

A plan for engaging the community at all levels (teens, parents, youth groups, children's rights organizations, non-governmental organizations, community-based organizations, politicians, policy makers, decision makers, elders, community opinion leaders, religious leaders, and the media) should be considered. In addition, along with existing community advisory board structures, consideration should be given to establishing a teen community advisory board. Structures other than a community advisory board may, however, be needed to engage the adolescent community and those committed to adolescent issues. It would be ideal to initiate communications with adolescents early on during the planning, preparedness, background data collection, and protocol development stages.

Finally, it would be useful to explore strategic opportunities and collaborative partnerships with adolescent-oriented organizations and non-vaccine groups in communities in which other HIV prevention research is ongoing.

In conclusion, this position paper outlines the current key issues and considerations, as well as the recommendations of expert consultants, to assist national regulatory authorities, ethics committees, public health authorities and broad communities involved in HIV vaccine trials in their deliberations and decision making when faced with the challenge of approving HIV vaccine clinical trials with adolescent trial participants.

It is generally understood that adolescents, before the initiation of sexual activity and exposure to any risk of HIV, will be the primary target for any public health intervention involving a successful HIV vaccine. It is therefore imperative to include adolescents as early as possible in HIV vaccine trials for products that might have an indication for use in both adults and adolescents, such as those intended to prevent the sexual transmission of HIV. Therefore, the generation of data relevant for adolescents is essential to support timely regulatory decision making for licensure/registration so that unnecessary delays in the future access of adolescents to a successful HIV vaccine can be avoided.

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References

1. UNAIDS/WHO. *AIDS epidemic update: December 2006*. Available at: http://www.unaids.org/en/ Accessed: July 2007.
2. UNAIDS. *2006 Report on the Global AIDS epidemic*. Available at: http://www.unaids.org/en/ Accessed: July 2007.
3. WHO/UNAIDS expert group. **Gender, age, and ethnicity in HIV vaccine-related research and clinical trials: report from a WHO/UNAIDS consultation, 26–28 August 2004, Lausanne Switzerland**. *AIDS* 2005; **19**: w7–w28.
4. Duerr A, Wasserheit JN, Corey L. **HIV vaccines: new fronteers in vaccine development.** *Clin Infect Dis* 2006; **43**:501–511.
5. McMichael AJ. **HIV vaccines.** *Annu Rev Immunol* 2006; **24**: 739–769.
6. Rodriguez-Chavez IR, Allen M, Hill EL, Sheets RL, Pensiero M, Bradac JA, D'Souza MP. **Current advances and challenges in HIV-1 vaccines.** *Curr HIV/AIDS Rep* 2006; **3**:39–47.
7. Spearman P. **Current progress in the development of HIV vaccines.** *Curr Pharm Des* 2006; **12**:114–1167.
8. Girard M, Osmanov S, Kieny M-P. **A review of vaccine research and development: the human immunodeficiency virus (HIV).** *Vaccines* 2006; **24**:4062–4081.
9. Society for Adolescent Medicine. **Guidelines for adolescent health research**. *J Adol Health* 2003; **33**: 396–409.
10. World Medical Association Declaration of Helsinki. *Ethical principles for medical research involving human subjects, 2004*. Available at: http://www.wma.net/e/policy/b3.htm. Accessed: July 2007
11. UNAIDS. Guidance document. *Ethical considerations in HIV preventive vaccine research, 2000*. Available at: http://data.unaids.org/Publications/IRC-pub01/JC072-EthicalCons_en.pdf. Accessed: July 2007.
12. Jaspan HB, Gray GE, Robinson AK, Coovadia HM, Bekker LG. **Scientific justification for the participation of children and adolescents in HIV-1 vaccine trials in South Africa.** *S Afr Med J* 2005; **95**:685–687.
13. Jaspan HB, Lawn SD, Safrit JT, Bekker LG. **The maturing immune system: implications for development and testing HIV-1 vaccines for children and adolescents.** *AIDS* 2006; **20**:483–494.
14. Milford C, Wassenaar DR, Slack CM. **Resources and needs of research ethics committees in Africa: preparations for HIV vaccine trials.** *IRB* 2006; **28**:1–9.