Protecting South Africa's children from HIV; giving them our best shot

Heather B. Jaspan[a*], Linda-Gail Bekker[a], Catherine J. Grant[b], Catherine A. Slack[b], Ann E. Strode[b] and Jessica R. Berwick[a]

The development of an effective HIV vaccine is a global health priority. The highest rates of new HIV infections in South Africa occur amongst the youth, and a vaccine will be vital to reduce incidence. Recent debate about the inclusion of adolescents in HIV vaccine trials, both internationally and nationally, is particularly relevant to South Africa, which harbours more HIV-infected people than any other country. To date, no preventative HIV vaccine trials have included adolescents. Vaccine trials in these age groups are constrained by unresolved ethico-legal issues, which are likely to delay licensure for adolescents should a favourable candidate vaccine be identified. There is a moral imperative to resolve these ethical and legal complexities in a broader debate, so that we may develop and test vaccines in a way that both protects and promotes the health of young people.

There are over five million HIV-infected people living in South Africa, more than in any other country. With just 0.7% of the global population, South Africa is believed to be home to more than 12.7% of the world's HIV-infected individuals.[1] The scale of the pandemic and the limited success of existing prevention efforts has therefore led the South African government and the private health sector to place a high priority on the development of an effective HIV vaccine.

According to UNAIDS, more than a quarter of the world's 40 million HIV-1-infected people are between the ages of 15 and 24, and 700 000 of the new infections that arose in 2003 were recorded in children under 15 years of age.[2] A review of sexual behaviour among young South Africans showed that at least half were sexually active by the age of 16, and that 50% to 60% reported never using condoms.[3] The Department of Health's 2003 antenatal survey reported that 8.5% of 15-year-olds were HIV seropositive.[4] The marked rise in positivity to 19.1% among 18-year-olds indicates that, in South Africa, teenage HIV infection is sexually acquired.

Since the late 1990s, new HIV infections have declined among those over the age of 25, while incidence in the 15-to-24 age category has remained high.[5] With the large majority of new infections occurring in South Africans below the age of 25, an HIV vaccine that can be administered to young people is urgently needed to control the spread of HIV. However, although there have been over 100 preventative HIV vaccine trials, with more than 30 currently in progress, none has included adolescents.

The development and testing of an HIV vaccine — where are we?

Preventative HIV vaccines have been in clinical trials internationally since 1988, and in South Africa since November 2003 (see www.hvtn.org and www.iavi.org). Live-attenuated and whole-killed vaccines are considered too risky for human trials, and vaccine development initially relied on the protein subunit approach used successfully for hepatitis B vaccination.[6] The envelope proteins of HIV were tested in clinical trials for several years until it became clear that these vaccines did not elicit a protective antibody response. Efforts were then redirected towards vaccine technology that induces a cellular immune response to more conserved (stable) regions of the virus.[8,9] However, since a correlate of immunity to HIV has not been identified, the immune response induced by a vaccine will remain unknown until the vaccine goes on trial.

There are physiological and immunological differences between children and adults that may affect the safety and efficacy of vaccines.[9] Some licensed vaccines have demonstrated that this maturation of the immune system results in age-dependent responses to vaccines and therefore must be considered in testing vaccines in clinical trials.

If we accept that HIV vaccines need to be tested in children, then two critical issues have to be addressed: first, at what point should clinical trials with adolescents begin and, second, will our ethical-legal framework allow such research with children?

It can take more than ten years for promising vaccines to be tested clinically in humans. It is generally accepted that safety and immunogenicity testing, which occurs prior to efficacy trials, is needed in adults before it is allowed in children.[10] However, there is a persuasive argument that testing of a preventative HIV vaccine in children should not be postponed until the completion of full-scale adult efficacy trials as this could delay the introduction of an HIV vaccine for children by as much as a decade. Globally, there are several HIV vaccines about to enter proof-of-concept or efficacy trials in adults. We have safety and immunogenicity data on adults for a large number of candidate vaccines, so that safety testing of selected vaccines in adolescents could begin immediately.

If we are to advocate for the simultaneous, staggered testing of HIV vaccines in adults and children, however, we need a coherent ethical-legal framework prescribing the terms of their involvement. On page 224 of this issue, Strode *et al.* discuss some of the ethical and legal complexities involved in enrolling adolescents in HIV vaccine trials. They argue that such trials may be lawful but there are gaps and inconsistencies in South African law, and in guidelines used by research ethics committees (RECs). They show that the new National Health Act (No. 61 of 2003) will help to address some of these gaps and inconsistencies, but the research provisions of the act have not yet gone into effect, and will create new inconsistencies once implemented. Despite the urgent need for national norms and standards governing research involving children, therefore, researchers, the Medicines Control Council, and RECs rely on existing laws that fail to address the subject.

Much has been done to prepare for the protected involvement of adolescents in HIV vaccine trials. Consultative workshops with investigators, legal experts and community representatives have established consensus on the need to include the youth in trials; the ethical-legal framework has been reviewed; ethical guidelines have been drawn up that support the vigilant inclusion of adolescents;[12] and incidence data are being collected. Yet unresolved issues remain that require immediate attention. Young people are a vulnerable target of the HIV epidemic and have a right to safe, timely and efficacious treatment that

[a]Desmond Tutu HIV Centre, Faculty of Health Sciences, University of Cape Town, P.O. Box 13801, Mowbray 7705, South Africa.

[b]The HIV/AIDS Vaccines Ethics Group, School of Psychology, University of KwaZulu-Natal, Private Bag X01, Scottsville 3209, South Africa.

*Author for correspondence.
E-mail: heather.jaspan@hiv-research.org.za

includes prophylactic vaccines. Legislation needs to be clarified to make their ethical participation in vaccine trials a reality.

1. World Bank (2004). *Data and Statistics.* Washington, D.C.
2. UNAIDS (2004). *2004 Report on the Global AIDS epidemic.*
3. HIV and sexual behaviour among young South Africans: a national survey of 15–24 year olds. Reproductive Health Research Unit, University of Witwatersrand; 2003.
4. *National HIV and Syphilis Antenatal Seroprevalence Survey in South Africa.* Department of Health, Pretoria; 2004.
5. Dorrington R.E., Bradshaw D., Johnson L. and Budlender D. (2004). *The Demographic Impact of HIV/AIDS in South Africa. National indicators for 2004.* Centre for Actuarial Research, South African Medical Research Council and Actuarial Society of South Africa, Cape Town.
6. The rgp120 HIV Vaccine Study Group (in press). Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *Journal of Infectious Diseases.*
7. Mwau M. and McMichael A.J. (2003). A review of vaccines for HIV prevention. *J. Gene Med.* **5**, 3–10.
8. Graham B and Wright P. (1995). Candidate AIDS vaccines. *New Engl. J. Med.* **333**, 1331–1339.
9. Jaspan H.B., Lawn S.D., Safrit J.T. and Bekker L.G. (in press). The maturing immune system: implications for development and testing HIV-1 vaccines for children and adolescents. *AIDS.*
10. McClure C.A., Gray G., Rybczyk K. and Wright P.F. (2004). Challenges to conducting HIV preventative vaccine trials with adolescents. *J. Acquir. Immune Defic. Syndr.***36**, 726–733.
11. World Medical Association. Declaration of Helsinki (2002). *Ethical Principles for Medical Research Involving Human Subjects.* Available at http://www.wma.net/e/policy/63
12. Medical Research Council (2004). *Guidelines on Ethics of Medical Research: HIV Preventative Vaccine Trials.* Cape Town. Online: http://www.sahealthinfo.org/ethics/ethicsbook5.pdf ❑