

# Adolescents and HIV clinical trials :ethics, culture, and context

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## Abstract

One quarter of HIV infections globally occur among young people 15-24 years of age and more than half of all new infections are to people younger than 25 years. Clearly, there is a need to identify and implement effective HIV prevention strategies among at-risk teens. Some of the most effective options for slowing the epidemic are biomedical and several promising methods are in development, including microbicides, vaccines, and pre-exposure prophylaxis (PREP) or the daily use of antiretrovirals to prevent the acquisition of HIV. There is widespread reluctance to enroll minors in such biomedical prevention trials due to concerns about vulnerability related to physical maturity, experiential maturity, and diminished autonomy as well as legal and social challenges that vary across and within nations. However, excluding minors from trials misses an important opportunity to evaluate the effectiveness, acceptability, and safety of innovative interventions under the best conditions for identifying and resolving potential problems. The challenges of including minors in HIV prevention trials are highlighted via the example of one rural South African community that has been particularly devastated by the HIV epidemic.

**Keywords:** HIV, prevention, research, adolescents, South Africa

UNAIDS estimated that 40 million people were living with HIV at the end of 2004 ([UNAIDS, 2005](#)). Approximately one quarter of infections occur among young people 15-24 years of age and that more than half of all new HIV infections are to people younger than 25 years ([UNAIDS, 2004](#)). HIV prevalence and incidence rates among young people are hard to come by, but those available for women attending antenatal clinics indicate that sexually active young women in sub-Saharan Africa are often at particularly high risk. In some areas more than 10% of girls ages 15-19 years and one-quarter to one-third of young women ages 20-24 years are infected with HIV ([UNAIDS, 2005](#)).

The rural community of Vulindlela, 150km west of Durban, South Africa is a stark example of this crisis. Vulindlela is in KwaZulu-Natal, the province at the epicenter of one of the worst HIV epidemics in the world with HIV prevalence among pregnant women utilizing antenatal services estimated at 47.1% and morbidity and mortality are rising rapidly ([Kharsany, Carrara, Frohlich, Abdool Karim, Abdool Karim, 2005](#)). Faced with such devastation, the local chief in Vulindlela sought out researchers at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) in Durban to help find a solution. Otherwise, he told them, he will soon be a leader with no people to lead.

The global UNAIDS HIV data and the Vulindlela prevalence data make a compelling case for the need to implement effective HIV prevention strategies among at-risk teens as well as adults. Existing HIV prevention options encompass a wide spectrum and the most successful programs combine a range of options that are tailored to both personal needs and the social context. Among the most common are behavioral interventions often described as the ABC approach: (A) abstain from sex and other risky behaviors such as drug use; (B) be faithful to one sexual partner (or, more accurately, practice mutual monogamy); and (C) use condoms with all sexual partners ([Shelton et al., 2004](#)). Behavioral interventions such as these can be highly effective but effectiveness is constrained by contextual factors including social, legal, ethical and economic.

Attention to social and structural issues has emerged relatively recently ([Parker, Easton, Klein, 2000](#)). For example, in an attempt to integrate gender concerns some interventions include improved education opportunities for girls and creating economic opportunities for women. Others focus on strengthening women's reproductive and sexual autonomy in ways that improve their overall health, as do measures to reduce violence against women, including rape. Development of local economic opportunities for men may reduce community-wide susceptibility by reducing the need for men to engage in migrant labor or long-distance trucking, both of which foster a flourishing sex industry with rapid turnover of sexual partners. However, such structural changes are difficult to design, implement, evaluate, and replicate.

In the short term, while solutions to the more challenging structural and behavioral issues related to HIV transmission are being sought, some of the most effective options for slowing the epidemic are biomedical. Examples include treatment of sexually transmitted infections that accelerate HIV transmission, prevention of mother-to-child-transmission with antiretrovirals, post-exposure prophylaxis (PEP) for targeted exposure events such as needle sticks and rape, and, most recently, male circumcision ([UNAIDS, 2005](#)).

More exciting still are several methods currently in development: microbicides that can be used vaginally or anally in addition to or instead of condoms; vaccines to either prevent infection or limit disease progression; and pre-exposure prophylaxis (PREP) or the daily use of antiretrovirals to prevent the acquisition of HIV. Importantly, all of these methods have the potential to be female-controlled and while they do not change the behavioral or structural dimensions of HIV risk for girls and women, they may safeguard women's health while those challenges are addressed by global, national, and community leaders. If proven safe and effective, these methods could help save the next generation from devastation by HIV---provided the necessary evidence is generated to support programs targeting youth.

## **Evaluating new HIV prevention technologies in adolescents**

Efforts to enroll adolescents in HIV prevention trials must be understood within a larger context of caution with regard to research participation by minors ([Mammel, Kaplan, 1995](#); [Rogers, Schwartz, Weissman, English, Adolescent Medicine HIV/AIDS Research Network, 1999](#)). Currently, there is widespread reluctance to enroll minors in biomedical prevention trials on the part of ethics committees, researchers, and others. At the same time, behavioral research with teens is increasingly constrained toward abstinence and delayed onset of sexual activity. Abstinence interventions are clearly preferable when effective; however, in the face of already-

high HIV and STI prevalence rates reliance on untested and restrictive abstinence messages may place the well-being of a whole generation at risk. A range of effective prevention options are needed. Excluding minors from biomedical prevention trials misses an important opportunity to evaluate the effectiveness, acceptability, and safety of innovative interventions under the best conditions for identifying and resolving potential problems.

That said, the inclusion of adolescents in clinical trials presents important ethical challenges ([Society for Adolescent Medicine, 1995](#)). First, there is the challenge of conducting research with individuals subject to multiple forms of vulnerability related to physical maturity, experiential maturity, and diminished autonomy. Second is the challenge of reducing risk in the face of vulnerability, for example, to what extent can we empower adolescents to use behavioral measures to protect themselves while simultaneously seeking to test a new intervention? Third, there are many legal and social challenges in undertaking clinical research with adolescents that vary across and within nations. We highlight and elaborate these challenges in the context of experiences in undertaking initial research efforts in one rural community that is particularly devastated by the HIV epidemic.

## Vulindlela

### Epidemiologic context

Vulindlela is a rural community of about 400,000 residents served by seven public health service clinics that offer comprehensive services. Unemployment rates are high, though limited opportunities exist with district projects implemented by the forestry industry. Due to the lack of local opportunities, many men live and work in the city during the week and return to their rural homes over the weekend.

AIDS is a new phenomenon in Vulindlela; information about it is incomplete and often conflicting. AIDS-related morbidity and mortality are having an overwhelming impact, and secrecy and fear are common. The disease has created challenges for many traditional practices, especially those related to the visiting of sick people and attendance of funerals. Where previously the community rallied around and supported families during these times, fear, shame and uncertainty in relation to AIDS has resulted in families now isolating themselves. Funerals have become a source of speculation as to the cause of death, with a closed coffin assumed to be indicative of an AIDS-related death. Family survivors are likely to find themselves caught in a new form of stigma and emerging discrimination.

Overall HIV prevalence among women attending antenatal clinics in Vulindlela increased from 26% in 2001 ([Frolich, Makhaye, Kharsany, Abdool Karim, Abdool Karim, 2004](#)) to 43% in 2004 ([Kharsany et al., 2005](#)). Also in 2004, 27% of those 19 years of age or younger and 55% of those aged 20-24 years were infected ([Kharsany et al., 2005](#)). The reasons for these high prevalence rates are varied and include early age of sexual debut, cervical ectopy, anal sex, and infection with other STIs. A variety of sexual coupling patterns place young women at risk including trends toward partnering with older men who are more likely to be infected, concurrent relationships and serial partnerships, low rates of condom use, and limited skills in negotiating

safer sex practices. Gender-based violence increases vulnerability, and poverty increases reliance on transactional sex for survival.

## **Challenges for HIV prevention research**

While these epidemiological data underscore an urgent need for highly effective HIV prevention interventions for youth in Vulindlela, a number of challenges exist for conducting trials of innovative interventions with this population. Most importantly, HIV risk is clearly linked to gender and age. With a quarter of women infected before they reach age 20, interventions must be feasible and highly effective among adolescent girls or significant prevention opportunities will already be lost. However, adolescents under age 18 are considered minors and therefore are subject to ethical and legal safeguards aimed at protecting their interests but simultaneously diminishing their autonomous decision-making. In South Africa, parental consent for minors is required for research participation; if the research presents greater than minimal risk then both parents must consent. If no parents or legal guardians are present, then the minor cannot be enrolled in the research ([Singh, Abdool Karim, Abdool Karim, Mlisana, Williamson, Gray et al., 2006](#)). These South African restrictions eliminate participation by minors in child-headed households, in those where the mother is present but the father absent, and those headed by grandmothers---all of which are common for minors in areas with high HIV prevalence rates such as Vulindlela. Additionally, and perhaps most importantly, while large numbers of adolescent women are clearly sexually active in Vulindlela, moral judgments about sexuality make it unlikely that many will seek parental guidance and permission for participation in HIV prevention research.

Counter concerns exist with regard to the participation of minors in research. There is a distinction between having the social autonomy needed for fully informed consent and the skills or competencies necessary for independent decision-making. Informed consent is complicated when young people have limited life experience to draw on for balancing risks and benefits. For younger adolescents, cognitive skills may not yet be fully developed and are therefore inadequate for some research-related decision-making. Thus, even in situations such as child-headed households where autonomous decision-making by minors is the reality, adolescents considering participation in research need the advice and support of mature adults who have their personal

## **Cultural Dynamics and HIV Prevention Trials**

As the description of Vulindlela above illustrates, effective intervention will require efforts at multiple levels because the factors that place people at risk for HIV are highly complex. Biomedical interventions such as vaccines, microbicides, and PREP generally do little to address behavioral, social, and structural dimensions of risk but nonetheless hold great promise of reducing rates of infection. As such, biomedical intervention trials can generate a great deal of controversy, for fear that the interventions will somehow bolster the very factors that generate risk. Due to such concerns, emerging models for prevention trials increasingly stress the integration of science and society.

As described in one such model ([MacQueen and Cates, 2005](#)), HIV prevention trials and other preventative clinical trials can be viewed as a continuum from the *conceptual* (identification of a

public health need and potential responses) to the *experimental* (development and implementation of research designs) to the *applied* (translation of research results into programs). This continuum, in turn, can be described in terms of five elements: (1) advocacy and policy, (2) community and civil society participation, (3) the clinical research enterprise, (4) acceptability by consumers, and (5) operations and program development. As has been amply demonstrated for HIV prevention research, effective prevention science requires coordination and integration of these five elements through all stages. For example, the successful implementation of the first phase 3 HIV vaccine trials were attributed to broad-based advocacy and policy support, effective community engagement, pre-trial acceptability and feasibility assessments, and site-specific capacity building ([Francis, Heyward, Popovic, Orozco-Cronin, Orelind, Gee et al., 2003](#)). Conversely, inadequacies with regard to one or more elements can undermine trials. For example, pre-exposure prophylaxis (PREP) trials with the antiretroviral tenofovir were closed prematurely in Cameroon and Cambodia when negative advocacy emerged and policy supports proved inadequate to overcome the criticisms, and in Nigeria when site procedures could not be brought into compliance with required standards ([Grant, Bookbinder, Cates, Clarke, Coates, Cohen et al., 2005](#)).

As the tenofovir example illustrates, community and civil society participation is perhaps one of the most challenging aspects of the prevention research continuum ([UNAIDS, 2006](#)). In order to pave the way for critically needed HIV prevention research in Vulindlela, CAPRISA researchers are building partnerships with the community on several levels. First, they are building trust with the community through the formation of a Community Research Support Group, by providing regular feedback to all stakeholders, and by holding public fora for discussion of HIV-related issues. Second, they are building relationships with volunteers as part of preparedness for future HIV prevention trials. Third, they are building trust in scientists and research through regular meetings and on-going feedback about what they are learning in their research. Lastly, by jointly developing a long-term, comprehensive research agenda they are establishing trust as an organization that is committed to Vulindlela's future.

## Conclusion

Vulindlela exemplifies the magnitude and complexity of the HIV epidemic but the challenges it presents are not unique. The toll of the HIV epidemic on the world's youth and especially on adolescent women make it imperative that we find ways to protect them from infection while we simultaneously address the social, political, and economic factors that generate vulnerability and perpetuate risk. The underlying dynamics may vary from Africa to Asia to the Americas and Europe but the vulnerability of youth is global. Innovative approaches to support culturally-informed and culturally-responsive HIV prevention trials among adolescents need to be developed. Doing so will require effort along several paths simultaneously. First, we need to give explicit attention to all of the elements that impact on the long-term success of HIV prevention research: policy, community, scientific, acceptability, and programmatic. This attention must further be cognizant of the types of questions and issues that can be effectively addressed across the research continuum, from conceptual to experimental to applied so that research is not hindered by a failure to adequately address concerns across the elements. Second, greater emphasis needs to be given to developing and evaluating effective models for collaborative, participatory, and interdisciplinary research approaches. Third, we need to develop mechanisms

that support all stakeholders in their efforts to respond to emergent issues along the research continuum. Fourth, we need to enhance our efforts at trust-building, communication, and fair benefits for research communities. Last but certainly not least, we need funding mechanisms that help us accomplish the necessary work.

## Footnotes

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