

ADOLESCENTS: THE MISSING COHORT

Adolescents⁷ make up a significant percentage of people infected with HIV around the world. But in nearly two decades of clinical research, adolescents have generally not been included in human trials of AIDS vaccine candidates. Almost all candidates have been tested in people over the age of 18.⁸

Unless adolescents are included in clinical trials, they likely won't have timely access to an effective AIDS vaccine when one is developed and licensed. That would not only deny young people of an important HIV prevention tool, but it would also hamper efforts to stop the AIDS pandemic.

“If we had a vaccine and it was only approved in those over eighteen, we would be missing at least twenty-five percent of the new infections in the United States and many more internationally,” says Bret Rudy, director of the adolescent HIV clinic at Children’s Hospital of Philadelphia and a national leader in HIV prevention for adolescents.

As it gears up for large international trials over the next five to ten years, the AIDS vaccine field needs to be more deliberate about addressing the issue. The following steps need to be taken now:

- **Strategic plans.** Sponsors of clinical trials—including the US government’s HIV Vaccine Trials Network (HVTN), the International AIDS Vaccine Initiative (IAVI), the South African AIDS Vaccine Initiative (SAAVI), and European Vaccine Effort Against AIDS (EuroVac)—need to develop strategic plans for the inclusion of adolescents in clinical trials. It may be too soon to begin enrolling adolescents, but plans to do so must be in place.
- **Regulatory advice.** The US Food and Drug Administration (FDA) needs to hold an informal meeting with AIDS vaccine trial sponsors to discuss the minimum criteria for an adolescent indication of an AIDS vaccine proved efficacious in adults. Without such guidance, it will be difficult for trial sponsors to develop intelligent plans. Similar meetings should occur with regulatory bodies in other countries such as South Africa. A key issue is whether regulatory bodies will require a Phase 3 study involving adolescents in order to approve an adolescent indication.
- **Coordination with existing prevention programs.** No vaccine trial that includes adolescents can be conducted without strong HIV prevention programs specifically targeted at youth. A number of youth programs exist or are being created in both the developed and developing world. AIDS vaccine trial sponsors need to link up with these programs now so they can include them in their strategic plans.

- **Learn from private-sector experience with other STD vaccines.** Important new ground is being broken by GlaxoSmithKline in testing a vaccine against genital herpes among adolescents, and by Merck & Co., testing a vaccine against human papilloma virus among adolescents. AIDS vaccine developers need to pay attention to these path-setting trials of STD vaccines among young people. Both firms have important lessons to pass on about the inclusion of adolescents in AIDS vaccine trials.

The potential benefits to youth of an AIDS vaccine

Of course, everyone will benefit from development of an effective AIDS vaccine, but adolescents especially so because they represent such a large proportion of people infected with HIV.

In sub-Saharan Africa, for example, about ten million of the region's thirty million people living with HIV are between the ages of 15 to 24. Among the young people, two-thirds are girls or young women.⁹ "Adolescent girls in high-prevalence countries in Africa are at significantly higher risk of acquiring AIDS. In some communities, as many as 20 percent of the girls aged 15 to 19 are infected compared to 5 percent of boys the same age,"¹⁰ says the US State Department in its new five-year \$15 billion plan to combat AIDS in sub-Saharan Africa and the Caribbean.

In the United States, a recent study by the Centers for Disease Control and Prevention (CDC) estimates that approximately 15,000 of the 40,000 new HIV infections reported to public health officials in 2000 were among young people aged 15 to 24.¹¹

Given the number of youth at risk, it would be unethical not to enroll them in clinical trials of an AIDS vaccine from which they could greatly benefit. Although international guidelines call for the protection of children from abuse in medical research, the guidelines are equally insistent that children should not be excluded from research that could benefit them.

As the Society of Adolescent Medicine observes, "The interests of justice demand that adolescents not be exploited for the benefit of others, but also that adolescents not be excluded from participation in research that may have direct or indirect benefit."¹² AIDS vaccine trials are an important case in point.

The challenges of enrolling adolescents

It is one thing to endorse the enrollment of adolescents in AIDS vaccine clinical trials and another to actually enroll them. The challenges include getting the informed consent of parents while honoring the privacy rights of the adolescent; fear that youth taking part in AIDS vaccine trials will engage in risky behaviors; the social risks associated with of vaccine-induced seropositivity; and the recruitment and retention of young people, who characteristically live busy and unstructured lives or who may be alienated from the medical system.

Issues are complex for any type of vaccine testing in adolescents. But for AIDS vaccines, there is added complexity. HIV is a sexually transmitted disease that carries enormous social stigma, particularly in the developing world, and among racial minority youth in the United States who are among those most at risk.

Working through these issues will take clear thinking, collaboration with young people and organizations that represent them, and political courage in the face of a growing conservative ideology promoting an abstinence-only approach to HIV education among young people attending US public schools. “Yes, there are challenges, especially ethical and logistical challenges,” says Craig Wilson, professor of pediatrics at the University of Alabama at Birmingham and chair of the US government’s Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). “But the overriding ethical imperative is that we have an HIV vaccine that can be given to adolescents.”

What follows are key challenges and AVAC recommendations.

Ethics

Under both international and US guidelines,¹³ children—including adolescents—are regarded as a “vulnerable” population that must be accorded special protections from exploitation and physical or emotional harm during the course of a clinical trial.

For adolescent girls, there may be additional vulnerabilities. “In some cultures, adolescent girls may not be able to exercise true autonomy in light of gender norms and the influence of their parents or partners,” the World Health Organization advises in its guidelines on conducting vaccine trials among children in developing countries.¹⁴

Because of these and other vulnerabilities, ethical guidelines lay out certain protections for children that extend beyond what is required for adults. Extrapolating from these, it is possible to infer what practices Institutional Review Boards, which must approve clinical trials, are likely to require in order for adolescents to participate in AIDS vaccine trials:

- Adolescents themselves must agree to take part in the clinical trial.
- At least one of the adolescent’s parents (or guardians) must give their fully informed consent for the adolescent to take part in the trial.
- The community in which the trial takes place should discuss and agree on the inclusion of adolescents before adolescents are enrolled.
- No vaccine should be given to adolescents unless it has first been given to a sufficient number of adults to insure that it is safe.
- Large numbers of adolescents should be enrolled in a vaccine trial only when it appears that the particular vaccine candidate being tested in adults shows promise of working in Phase 2 studies.

While it may take time and effort to implement such safeguards, they are all do-able. Indeed, most can be met with good planning and quality counseling and education programs—a practice to which leading trial networks already adhere.

The most daunting challenge is likely to be securing informed consent of the parent while also protecting the privacy of the adolescent. The consent process may force adolescents to tell their parents—and researchers—whether they are sexually active. In some cultures and some families, an admission of sexual activity could have adverse consequences for the adolescent.

But there are ways around the problem. If it were unnecessary to enroll adolescents in Phase 3 trials—which are conducted among people at high risk of HIV—there would be no need to screen young people for trial participation based on sexually active status. Trials could be conducted among adolescents generally, no matter what their risk.

On the other hand, if adolescents need to be enrolled in Phase 3 trials, researchers can determine whether a young person is sexually active short of asking directly. For instance, a previous STD diagnosis might be an enrollment requirement; or for young women, a previous pregnancy.

In some communities, the average age of sexual debut may be so low that researchers can simply assume that enough adolescents are sexually active in a particular population to include them in a clinical trial. For example, a University of Cape Town survey conducted among 500 youth aged 13 to 18 in Masiphumelele—an informal community south of Cape Town—found that fifty percent of the youth were sexually active by the age of fourteen, the majority knew about HIV but did not use condoms, and most had multiple sex partners.

Whatever approach is taken will largely depend on whether Phase 3 trials will be necessary for adolescents. That's why it's so important that the FDA and other regulatory bodies step forward now to share their thinking on the issue in a consultation with AIDS vaccine trial sponsors.

There is precedence for such consultation. Last year, the FDA met with AIDS vaccine developers to broadly discuss the criteria the agency would need to approve a therapeutic AIDS vaccine to treat people who are already infected.¹⁵ A similar meeting should now convene to discuss complex regulatory issues related to adolescent indications for an AIDS vaccine tested primarily in adults.



By the age of 22, one in four South African women has HIV. In South Africa's Tembisa township, a 21-year-old mother with HIV nurses her six-week-old baby, who is also infected.

Source: Survey of 11,904 South African youth aged 15 to 24 by the Reproductive Health Research Unit at the University of Witwatersrand, 2004.

Photo courtesy of Mujahid Safodien, *The Johannesburg Star*.

Discouraging risky behaviors

Another big challenge to overcome is concern that adolescents, if enrolled in AIDS vaccine clinical trials, could view participation as a green light to engage in risky behaviors, such as having unprotected sex with multiple partners.

So far, in the two Phase 3 trials of AIDSVAX—the only vaccine that has yet completed large efficacy tests—this has not proven to be a problem among adults. However, it may be a problem among adolescents who are just becoming sexually active.



With well-executed youth-oriented HIV prevention programs, however, this concern can be overcome. Such programs already exist or are in the making in fifteen US cities involved in the federal government's Connect-to-Protect program, which is targeting specific neighborhoods for stepped-up HIV prevention among adolescents.

The program, which will run five years, uses demographic data to locate the most HIV-impacted neighborhoods in the targeted cities, many of them African American, and then mobilizes community-based organizations in an intensive campaign to prevent HIV among adolescents in those areas.

“Don't expect families to let their healthy, HIV-negative children roll up their sleeves and get inoculated if all you've got to offer the community is a vaccine that might work in some distant future,” says Audrey Smith Rogers, director of the maternal and child division of the National Institute of Child Health and Human Development, which is overseeing the program along with the CDC. Rogers adds, “But the community might accept it if it's one component of a much broader HIV prevention agenda.”

Adolescent trials should also be conducted in conjunction with enhanced HIV prevention activities targeted at youth in developing countries. Such activities will be rolling out in the most impacted countries in sub-Saharan Africa and the Caribbean over the next five years under the bilateral PEPFAR program. Prevention initiatives have also been launched through the Global Fund.

In South Africa, the Kaiser Family Foundation's “loveLife” initiative represents the world's largest HIV prevention program for youth. Vaccine researchers could locate adolescent trial units near the network of youth centers that loveLife has set up across the country. That would ensure that HIV prevention was an integral part of adolescent trials.

Vaccine seropositivity

Another key challenge is explaining to adolescents and parents that, if participants are in the active arm of a trial, they will likely test HIV seropositive on standard assays—even though they are not actually infected with HIV.

While possible vaccine-induced seropositivity discrimination is a concern for adults, it may be more of a concern for adolescents who are just embarking on adult life. At issue may be a young person's ability to enter military service, for instance, or, in the case of adolescent girls in sub-Saharan Africa, to marry and remain a valued member of a family unit. The very fact of participating in an AIDS vaccine trial may subject young people to stigma and discrimination among friends, family, and others.

AIDS vaccine researchers need to make sure that systems are in place to verify that a positive test stems from vaccine-induced antibodies, rather than an actual infection. Also, needed are programs to combat discrimination against anyone enrolled in an AIDS vaccine trial—whether they test HIV seropositive or not.

Each community will need to decide what measures will work best in the local context. One option may be an ID card specifying that the adolescent has taken part in a trial and may test positive on HIV antibody tests, though is not infected. Additional measures could be a special office where trial participants, including adolescents, can take their complaints if they experience discrimination; and a concerted effort to provide test kits at vaccine trial sites that can distinguish between vaccine-induced positivity and an actual infection.

Recruitment and retention

Recruiting HIV-negative adolescents into AIDS vaccine trials—and retaining them—will also be a challenge. Given the importance of peer pressure, many young people may not want to be enrolled in a study that involves a disease associated with homosexuality, intravenous drug use and what some people regard as sexual promiscuity. Many youth may not want to participate for fear they will have to talk with their parents about sex. Others may be too busy to keep clinic appointments, while some may lead complex lives marked by homelessness, drug use, incarceration and frequent changes of address.

Among some youth, deep mistrust of government-sponsored medical research may exist because of past ethical lapses, such as the infamous Tuskegee syphilis study involving African-American adults who were denied penicillin while US government scientists studied the course of their syphilis infection. The study ended in the 1970s, but its legacy lives on in the African-American community.

Despite these sensitivities, Merck and GlaxoSmithKline are demonstrating that it is possible to recruit large numbers of adolescents into clinical trials of vaccines aimed at preventing infection with two other sexually transmitted diseases—human papilloma virus (HPV), the leading cause of cervical cancer and a cause of genital warts, and herpes simplex virus (HSV) type 2, which causes genital herpes and genital ulcers.

Admittedly, these viruses don't carry the same stigma as HIV, nor do they typically represent a health pandemic. Still, the fact that they are sexually transmitted viruses means that testing vaccines against

these infections among adolescents is not as simple as enrolling youth to test vaccines against such common childhood diseases as measles and mumps.

In face of the challenge, Merck has managed to enroll between 5,000 and 6,000 adolescents, aged 9 to 18, in a Phase 3 trial of its HPV vaccine. All told, the vaccine is being tested among 25,000 people in thirty countries. Likewise, Glaxo recently initiated several studies of its HSV vaccine, which will enroll approximately 7,000 young people aged 10 to 17.

Both companies have turned to large pediatric practices in developed countries to recruit volunteers. Glaxo has also recruited from public schools in Canada for trial participants. Merck has enrolled adolescents at trial sites in both developing and developed countries—including the U.S., Canada, the United Kingdom, Colombia, Peru, Mexico, Thailand and the Philippines—through recruitment efforts at large public health clinics, private clinics and non-governmental organizations working in working-class and migrant communities.

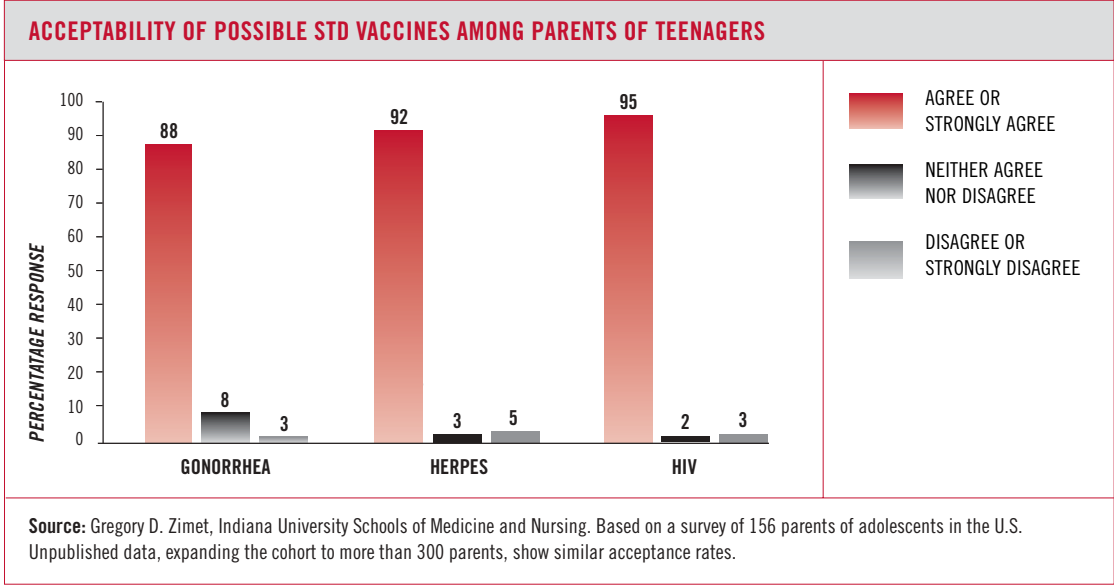
Before enrolling adolescents, both companies consulted widely with experts on adolescent health. “It’s very difficult to explain the studies to a ten or eleven-year-old,” says Gary Dubin, the Glaxo physician in charge of the clinical development program. To best do that, the company developed a youth “informed assent form,” in which a youngster gives his or her written approval to take part in the trial. This was supplemented by age-appropriate educational brochures and a website catering to pre-teens. Of course, parents were also asked to sign consent forms.

Merck developed a strategy aimed at helping take the stigma out of HPV by depicting it in brochures, posters and booklets as a medical problem that can lead to cervical cancer, not as an infection freighted with undertones of sexual promiscuity. “This took it out of the realm of an STD and made it into just another disease that people get,” explains Eliav Barr, senior director of the HPV vaccine clinical research program. Barr said recruitment was strongest in developing countries because of relatively high prevalence of cervical cancer.

The experience of these companies provides helpful lessons for the AIDS vaccine field as it moves toward the inclusion of adolescents in clinical trials. Undoubtedly, Glaxo and Merck, both of which are developing AIDS vaccines as well, will make use of their STD trials experience to consider inclusion of adolescents in their HIV trials. Other trial sponsors need to draw on the companies’ accumulating experience and glean from it information that will better inform the AIDS vaccine field.

If we make it, will they come?

Fast forward to the day that the world finally has an effective AIDS vaccine, licensed for use not only in adults, but also in adolescents. Will parents and their teenagers go for it?



That was the question asked by Gregory D. Zimet and colleagues at Indiana University Schools of Medicine & Nursing as part of a federally-funded study to examine predictors of parental acceptability of STD vaccination for their adolescent children. The study involved interviews with 156 parents of adolescents aged 12 to 17 who accompanied their children to appointments at urban adolescent health clinics and primary-care pediatric offices.

In the survey, parents were asked to record their responses to a statement about the acceptability of vaccines against gonorrhea, genital herpes and HIV/AIDS. For HIV/AIDS, the statement was: “If a safe and effective vaccine for preventing HIV/AIDS was available, I would get my child vaccinated.” Parents were asked to respond on a five-point scale, ranging from “strongly disagree” to “strongly agree.”

The responses—at least among this cohort of American parents—were overwhelmingly positive. And of the three vaccines, the vaccine for HIV/AIDS had the most support. (See chart this page.)

Of note, Zimet found important factors that predicted a favorable response: whether the parents themselves had experienced an STD infection, the degree to which the parent believed that their adolescent child was vulnerable to an STD infection in the next five years, and the anticipated negative effect on their child of learning they had contracted an STD. The one factor that predicted less acceptance of the vaccine was the fear that it would lead the teenager to engage in unsafe sexual activity. “The influence on sexual behavior—more partners and less use of condoms—is a real disincentive,” Zimet explained. “For HIV vaccine researchers, it’s a justifiable concern to anticipate.”