

6. The Question of Enrolling Adolescents

What to do about teenagers?

Adolescents comprise a potentially large and extremely important group of prospective microbicide users. Traditionally, there has been much reluctance to involve adolescents in clinical trials, especially younger adolescents—and indeed, vexing questions make this matter exceptionally complex.

Adolescent girls differ from adult women both biologically and behaviorally. These differences potentially affect the effectiveness and, possibly, the safety of microbicide products. Such differences will likely affect whether, when, and how effectively adolescents can make use of future microbicides.

Our general wish to protect adolescents from research-related risks has a serious down side with respect to microbicides. As a result, we know far too little about the likely acceptability, safety, or efficacy of products among an alarmingly susceptible user group that is globally at great risk of infection. Fundamentally, the ethical question boils down to: Is there a compelling need to establish the safety and effectiveness of candidate products for younger adolescents as distinct from adult women; and if so, are these reasons sufficiently compelling to warrant the exposure of younger adolescents to research-related risks?

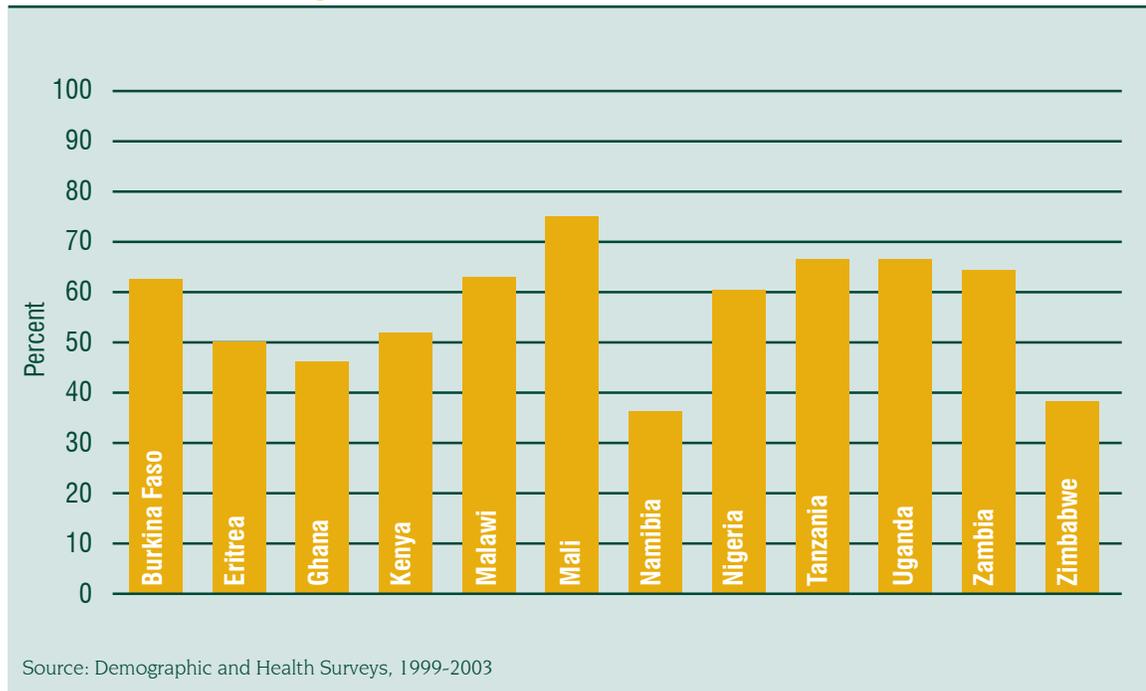
The Consultation broke down this dilemma into two interrelated questions. First, what are the behavioral and biological factors that could potentially alter the safety and effectiveness profile of microbicides in younger adolescents compared to older women? Second, what are the ethical, legal, and practical challenges if younger adolescents are to be enrolled in clinical trials?

Adolescent vulnerability

During adolescence, a young person's body and cognitive abilities develop rapidly. Hormonal changes are dramatic. The capacity to reason continues to evolve from the very concrete toward understanding of abstraction. By mid adolescence (normally around the ages of 14 to 16), most adolescents' cognitive abilities are roughly the same as biologically mature adults. Intellectually, they are able to understand issues such as long-term risks and the benefits of research. Yet there is another side to the coin. Adolescents of the same age are also frequently inclined toward risk taking, they are often resistant to adult advice, and they are acutely sensitive to peer influence. These factors can affect their understanding of risks and their capacity to make consistently sound judgments about their long-term best interest.

Young people around the world typically begin to engage in sexual activity during



FIGURE 3: Percentage of Women (ages 20-49) Who Had First Sexual Intercourse Before Age 18

➔ 28

these same years. In the United States, more than 60 percent of young women have had sex by the time they are in twelfth grade.¹ In sub-Saharan Africa, the percentage of women 15 to 19 who have had sexual intercourse ranges from 30 to more than 70 percent.² (Figure 3). Yet the percentage of 15- to 19-year-old women in sub-Saharan Africa who used a condom at their most recent sexual encounter is very low—well below 20 percent in all but two countries shown in Figure 4.³

Sexual exposure, together with the behavioral and biological realities of adolescence, combine to place young women at especially high risk of STDs, including HIV. In the United States, 15- to 19-year-olds have the highest rates of chlamydia and gonorrhea among women of all ages.⁴ Rates of the human papillomavirus infection (HPV) are highest among women under the age of 21.⁵ Young women and girls constitute nearly two-thirds of 15- to 24-year-olds living with HIV/AIDS in



¹ Centers for Disease Control and Prevention. Youth Risk Behavior Surveillance, 2003. In: Surveillance Summaries, May 21, 2004. *Morbidity and Mortality Weekly Report*. 2004; 53(No.-SS-2):1-100.

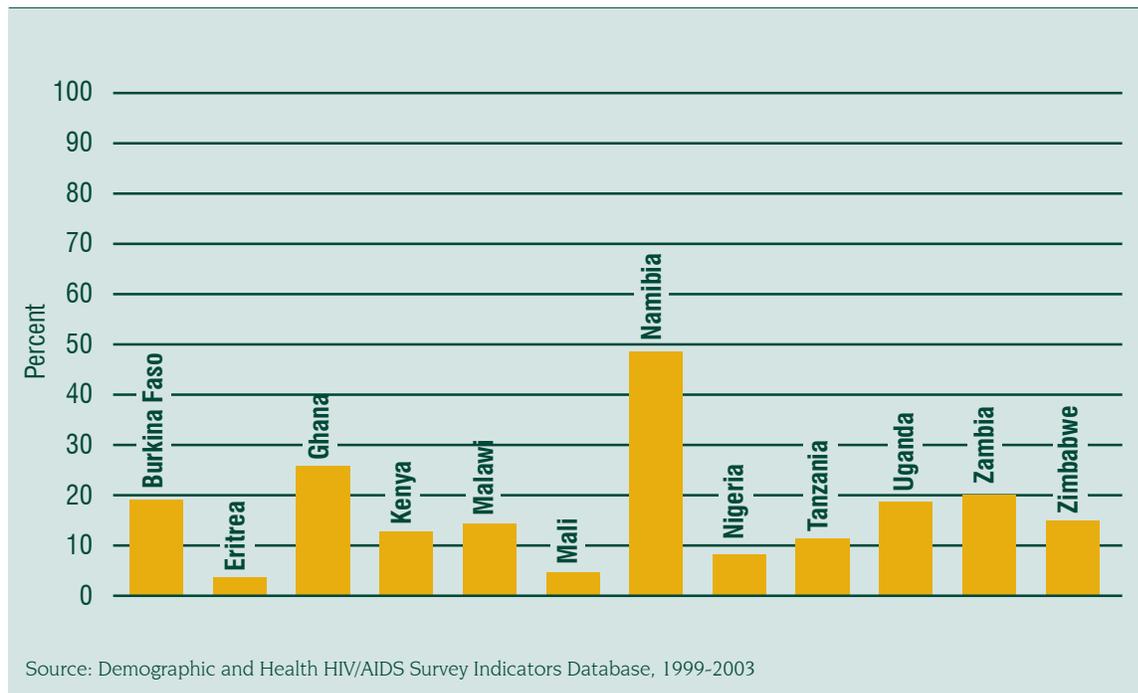
² Data from various Demographic and Health Surveys, Calverton, MD: ORC Macro International. Available at: <http://www.measuredhs.com>. Accessed March 21, 2005.

³ Ibid. ORC Macro, 2005. MEASURE DHS STATcompiler. Available at: <http://www.measuredhs.com>. Accessed March 21, 2005.

⁴ Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance*, 2003. Atlanta, GA: US Department of Health and Human Services, September 2004. Available at: <http://www.cdc.gov/std/stats/03pdf/SFAdoles.pdf>.

⁵ Stone KM, et al. Seroprevalence of human papillomavirus type 16 infection in the United States. *Journal of Infectious Diseases*. 2002;186:1396-1402.

FIGURE 4: Percentage of Young Women (ages 15-19) Who Used a Condom in Their Most Recent Sexual Encounter



developing countries. In some parts of sub-Saharan Africa, the infection rate of girls outnumbers that of boys by ratios of 6 to 1.⁶

Are adolescents sufficiently different from adults to warrant separate data?

Without doubt, adolescents represent a critically important user group for microbicides: Their behavior puts them at risk, and they bear a disproportionate share of the global health burden of STDs and HIV. But do those under 18 necessarily have to be enrolled in clinical trials? Is it reasonable and sufficient to extrapolate safety and effectiveness data derived from women over 18? If not, how should the microbicide community handle the ethical and legal challenges of enrolling younger adolescents in trials?

The Consultation sought out the expertise of Anna-Barbara Moscicki, associate director of the Division of Adolescent Medicine at the University of California San Francisco, to address the questions of biology and behavior. Dr. Moscicki argued forcefully that the biologic and behavioral differences between young adolescents and older women justify separate safety and effectiveness data on younger adolescents. As she explained, the cervixes of younger adolescents are not fully mature, making them biologically more susceptible to STDs. Adolescents' menstrual patterns also differ from adult women, as some 80 percent of adolescents will have cycles without ovulation within four years after menarche. Without ovulation, adolescents lack progesterone, which may influence the vagina's local immune responses. Box 4



⁶ UNAIDS. *World AIDS Campaign 2004: Women, Girls, HIV and AIDS*. Geneva: UNAIDS; 2004.



BOX 4: Biologic Differences in Adolescent Versus Adult Women

In adult women, the inner neck of the cervical canal (known as the endocervix) is lined with single-cell columnar epithelium. The outer part of the cervix (ectocervix), which is exposed to STDs and other pathogens, is predominantly made up of a thicker, stronger squamous epithelium. In contrast, the fragile columnar cells of the endocervix extend down to the outer surface of the adolescent cervix (a condition known as ectopy), exposing this vulnerable region to trauma and pathogens via the vagina. The hormonal changes of puberty cause an increase in the acidity of the vagina and induce the columnar cells of the ectocervix to undergo a process known as metaplasia, which converts the fragile columnar cells into thicker, more protective squamous epithelium, thus helping safeguard the cervix from infections. This process, which takes several years, begins during puberty and is usually complete by the age of 24 or 25.

Adolescents' menstrual patterns also differ from adult women. Some 80 percent of adolescents will have cycles without ovulation within the first four years after menarche. Until they ovulate, adolescents lack progesterone. This may influence the vagina's local immune responses.

Before and during this metaplastic transition, a girl may be particularly vulnerable to infection. Columnar cells offer easier access to infection with the human papilloma virus, which then proliferates, stimulated by the process of metaplasia. A pubertal girl is also more vulnerable to chlamydia and gonorrhea, which preferentially adhere to the exposed columnar cells.

provides greater detail on some of these biological distinctions.

The behavior of younger adolescents also differs from adults in ways that could eventually affect how they will use microbicides. Such distinctions could become incredibly important when considering how to introduce and promote microbicides to teens.

Adolescents in clinical research

The prospect of including younger adolescents in research raises a tangle of legal, regulatory, and practical challenges.

In the first place, an essential tenet of ethical research is that participants must freely choose to participate. Those who consent (or whose consent is sought) must be able to understand the implications of information that is provided about the study.

Ethical guidelines have traditionally treated young people as "vulnerable," meaning their capacity to consent is limited and therefore requires special protection as a group. In the United States, for example, the code of federal regulations governing protection of human subjects does not distinguish between children and youth.⁷ Both groups are considered "vulnerable"; and like pregnant women or prisoners, are afforded special protections in research. The National Bioethics Advisory Commission recently recommended that US regulations be updated to avoid rigid categorization of whole categories of people as vulnerable and in need of special protections.

The challenge is one of balance. There is tension between the desire to recognize the emerging autonomy of adolescents and the need to protect them. Their not yet mature response to personal risk must be



⁷ Health and Human Services Regulations (45 CFR 46) entitled "Protection of Human Subjects."

recognized and weighed against the potential benefits from participation. Research involving adolescents must account for the particular characteristics of adolescents, including their tendency toward altruism, rebellion, and peer pressure, as well as their increased sensitivities around body image, privacy, and confidentiality.

The issue of parental consent

For federally funded research in the United States, adolescent participation in clinical trials requires permission from a parent or guardian, as well as the informed “assent” of the young person. Under specified conditions, local ethics review boards can waive the parental permission requirement. (No such waiver option exists in the federal regulations governing investigational research of the US Food and Drug Administration). Alternatively, they can require special accommodation.⁸

Parental permission requirements may create a barrier to young people’s participation in clinical trials of microbicides. As explained in Chapter 2, individuals participating in Phase 3 trials must be at high risk of HIV infection. To protect their privacy, young people may choose not to participate in trials if they believe that their sexual activity may be disclosed to their parents. For researchers, this provides a challenge. They must creatively devise screening and consent procedures that protect young people’s privacy while providing them with the benefits of being involved in research.



⁸ In some cases where parental permission is waived—because there are no parents in the young person’s life, or the parents are deemed unfit or incompetent—alternative means are established to protect the young person’s rights. Where a study protocol requires adherence to a rigorous schedule, for example, adolescents may be provided special help to fulfill requirements.

⁹ WHO Scientific and Ethical Review Group. *Guidelines for research on reproductive health of adolescents*. Geneva: WHO; 2000. Available at: http://www.who.int/reproductive-health/hrp/guidelines_adolescent.en.html.

The US regulatory stance toward required parental permission is more restrictive than the position brought forward by the Special Programme on Research Development and Research Training on Human Reproduction (known as HRP) within the World Health Organization (WHO). HRP guidelines observe:

There are no clear ethical justifications for excluding from research adolescent subjects below the age of legal majority. If there are reproductive health problems that are restricted to, or occur also in, adolescents that cannot be solved with existing knowledge, there is an ethical duty of beneficence and justice to conduct appropriate research to address these problems.

Unless specific legal provisions exist, consent to participate in research should be given by the adolescent alone. Capacity to consent is related to the nature and complexity of the research. If adolescents are mature enough to understand the purpose of the proposed study and the involvement requested, then they are mature enough to consent.

In such cases where adolescents are currently or are about to be sexually active, investigators commit no legal offence in undertaking research that promises a favourable benefit-risk ratio. However, where the law specifically denies decision-making authority to mature or competent adolescents below a given age, that provision must be respected (page 25).⁹



Trials in developing countries

The codification of ethical requirements in most Southern countries is far less developed than in the United States or Europe. Botswana, for example, has no laws or regulations addressing adolescent participation in research. So the age of maturity—that is, the age at which a woman can legally sign a contract—is often used to exclude women under 21 from clinical research without parental consent. Yet the prevalence of HIV among 18- to 20-year-old pregnant women is 25 percent in Botswana, and nearly a quarter of the women at risk of HIV infection are 12 to 20 years old.¹⁰ Excluding adolescents from microbicides research amounts to excluding a large percentage of the population at greatest risk.

The BOTUSA project, a joint initiative between the Botswana government and the US Centers for Disease Control and Prevention (CDC), is interested in enrolling younger adolescents in upcoming microbicide trials. To contextualize the issue, the project examined other kinds of laws and customs that define the age at which a young person in Botswana assumes adult roles and responsibilities. An 18-year-old, for example, can vote, operate a vehicle, purchase alcohol, or be tried for a crime as an adult. All adolescents may access family planning, be treated for an STD, or receive prenatal care without parental permission. A 16-year-old girl can legally consent to have sex, but she must be 21 to get an HIV test without parental permission or to enter into a legally binding contract.

In addition to the fundamental ethical question—the age at which most people are able to make sound judgments about participating in research—other reasons may dictate against involving adolescents without parental permission. For example, focus group research in Botswana revealed that enrolling adolescents without parental permission could alienate communities at the cost of losing support for the study. One proposal for enrolling adolescents *with* parental consent would be to recruit them into trials at postnatal care visits. With parents already aware that their teenage daughters have been sexually active, the researchers would ask parents for permission to screen the child for HIV (an eligibility criteria for microbicide trials), with the understanding that parents would not be apprised of their child's HIV status (unless the adolescent so wishes). The adolescent would make an autonomous decision on whether or not to enroll in the trial.

Constructing a way forward

Consultation participants agreed that establishing safety and effectiveness of microbicides among young adolescents is essential. Exactly how and when to collect this data, however, requires more in-depth consideration.

One approach would be to start with adults only in Phase 1 and 2 safety trials. Once a product candidate is shown to be safe for adults, combined Phase 1 and 2 trials could be undertaken with adolescents. If safety is confirmed, these young people could then



¹⁰ Smith DK, Chillag K, Tibe, K. Adolescent participation in microbicide trials: a view from Botswana. Presented at: The International Consultation on Ethical Issues in the Clinical Testing of Microbicides, October 23–24, 2003; Warrenton, Virginia.

be enrolled in a special adolescent-only arm of a Phase 3 trial or enrolled along with women over 18 in a traditional, two-arm Phase 3 trial. The problem is that integrating adolescents into an overall Phase 3 trial would probably not yield sufficient data on young adolescents to assess effectiveness in adolescents as a category, because the number of participants would still be too small for statistically significant conclusions.

Ultimately, a full Phase 3 trial among younger adolescents will likely be necessary because the effectiveness of microbicides, unlike vaccines, may be affected by the immunological environment and cervical ectopy common in younger girls. Moreover, the protection achieved with microbicides is very likely to be affected by age-related behavior. Participants recommended further exploration of this issue.

