8. Antiretroviral Treatment in Clinical Trials

HIV treatment in prevention trials

Reflecting a marked change from the past, provision of antiretroviral treatment (ART) has moved to the forefront of current debates on the ethics of HIV prevention trials. In the 1997 ethics symposium, discussion of ART was not even on the agenda, because ART was then considered too complicated and expensive for resource-poor countries. In recent years, however, antiretroviral drugs have improved and costs have significantly dropped. Treatment activism has increased, so the issue is widely being reexamined.

UNAIDS originally spearheaded the discussion on provision of ART, especially as it relates to those who seroconvert during vaccine trials. Between 1998 and 2001, UNAIDS organized regional consultations to discuss HIV treatment in the context of vaccine trials in Brazil, Thailand, and Uganda. However, delegates could not reach consensus on whether vaccine trials—as a matter of ethics—should guarantee access to ART to trial participants.

The UNAIDS Brazil consultation concluded that participants should receive the level of HIV treatment available in the country sponsoring the trial. This would mean ART for at least the duration of a trial, and longer if that could be negotiated. Delegates to the Thai meeting argued for a level to be decided upon by the host country. This would include monitoring, prevention, and treatment of opportunistic infections, and palliative care—though not necessarily ART. Whatever was to be provided should be made reasonably available for the lifetime of the participants. The Ugandan consultation concluded that the local standard of care should be respected. It found no imperative to provide a level of care consistent with that of the sponsoring country or with the highest level of care available in the world.

In 2000, UNAIDS declared, "Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy and the minimum to provide the highest level of care attainable in the host country."[1]

The pros of ART in the benefits package

Throughout these discussions, arguments have been made for and against making ART obligatory in the benefits package. The following arguments are in favor:

- Sponsors have an ethical obligation to offer the best care according to their resources.
- Participants in sponsor and host countries should receive equal care, not a double standard.

[1] UNAIDS. *Ethical Considerations in* HIV *Preventive Vaccine Research*. UNAIDS Guidance Document. Geneva: UNAIDS; 2004.

- Participants in the research deserve to receive the highest possible standard of care in light of the risks and burdens that they assume.
- Some participants might engage in risky behavior because of a common misconception—that the product provided during the trial guarantees protection. (This is referred to as the "therapeutic misconception."[2])

The cons of ART in the benefits package

These arguments have been made against the obligatory provision of ART:

- Promising ART might create an undue inducement to individuals who see themselves at risk but do not otherwise have access to treatment.
- Giving ART to trial participants might exacerbate local inequalities and create problems within families or communities.
- Most women involved in prevention trials are uninfected, so ART is not relevant to them. Providing other kinds of health services would be more beneficial to a much larger number of women.
- Host countries and communities have the sovereign right to determine the balance of risks and benefits that they are willing to accept. Furthermore, they should be able to ascertain which services they believe to be of maximum benefit and thus want included in their package.
- Governments might dodge commitments and responsibility to provide long-term care and ART treatment, especially if they believe the research sponsors will provide it.
- Exclusive focus on ART may divert attention and resources from less-studied aspects of HIV treatment and care that potentially affect greater numbers of people.
- If they have to assume a substantial additional expense because of obligatory ART, prospective sponsor governments might be disinclined to finance trials.

ART in the context of microbicide and vaccine trials

As the provision of ART has come within reach, those involved in HIV prevention trials are rethinking how ART should and will affect their research. Recent consultations have brought together a diverse spectrum of stakeholders to debate and develop coherent policies regarding access to HIV treatment in the context of prevention trials.[3]

Several vaccine networks and sponsors—including the HIV Vaccine Trials Network (HVTN), the South African AIDS Vaccine Initiative (SAAVI), and the International AIDS Vaccine Initiative (IAVI)—have committed to

[2] "Therapeutic misconception" is an ethical term that refers to a tendency among trial participants to wrongly assume that participation in the trial will necessarily benefit them personally. It frequently arises because people do not fully understand the difference between health care provision (where the patient can rightly assume that whatever is given is believed to work) and research (where clinicians are attempting to figure out if a new intervention will work). In prevention trials, the therapeutic misconception refers to people believing that the new product protects them, even though they have been counseled that the experimental product is unproven and that they may be receiving a placebo.

[3] The recent consultations include: the South African AIDS Vaccine Initiative (SAAVI) meetings in December 2001 and August 2002, the South African Microbicides Research Institute (SMRI) meeting December 2002, Global Campaign for Microbicides/ International AIDS Vaccine Initiative (IAVI) meeting in February 2003, the South African National Consultation in April 2003, and the WHO/UNAIDS meeting in July 2003.

providing ART to those who become infected during vaccine trials. In the words of SAAVI, "The question is not if, but how."

In the case of vaccines, the rationale for ART is scientific as well as ethical. Participants in vaccine trials need to be followed for several years to determine whether a vaccine that does not prevent infection nonetheless reduces the time to the viral set point or to disease. Over this extended period, the CD4 count of many individuals may deteriorate, and they may become symptomatic. Thus, participants may still be enrolled in vaccine trials when they become eligible for HIV treatment under WHO guidelines.

A question still being debated is *who* is responsible for providing the treatment—research sponsors, the host nation, or the sponsoring governments. A number of approaches to long-term treatment are being explored, including creation of treatment funds and insurance schemes. In 2004, IAVI held in-country consultations, first in Uganda and India, to develop plans for HIV treatment access. Their goals are to collaborate with those working on treatment—to prioritize vaccine research sites in ART scale-up efforts—and to explore joint ventures to create access to vaccines and treatment.

In July 2003, WHO/UNAIDS convened a consultation, HIV Treatment for Intercurrent Infections. This brought the vaccine and microbicide worlds together, along with social scientists, ethicists, community representatives, and donors. Together, they affirmed that providing ART conforms to several fundamental ethical principles: *beneficence*, by which researchers are obliged to maximize benefits to participants; *reciprocity*, which suggests that those who contribute important data to the study by becoming infected deserve something in return; and *justice*, by which participants in trials who seroconvert should be treated equally, regardless of their setting.

The WHO/UNAIDS consultation produced the following recommendations:[4]

- Trial participants who seroconvert during HIV prevention trials should have access to quality treatment and care, including ART.
- Before a trial starts, agreements should be reached among all the stakeholders on the level of care and approaches to treatment. This includes sponsors, researchers, communities, host governments, and industry.
- Funding mechanisms that will ensure continued treatment and care should be fully discussed and agreed on by the participating organizations.
- The trials should contribute to building local capacity, so that treatment and care can be accessed through local health and social services.
- Where the local health system is unable to provide adequate services, alternative mechanisms—for example, earmarking of funds for services—must be put in place.
- Although institutions like the World Bank and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (The Global Fund) do not finance basic research and clinical trials directly, they could nevertheless provide resources that help facilitate research, such as infrastructure, as well as treatment and care.

[4] WHO/UNAIDS. Treating People with Intercurrent Infection in HIV Prevention Trials: Report of a WHO/UNAIDS Consultation. *AIDS.* 2004;18(15):W1-W12.

- Research participants, partners, and family members found to be HIV positive at the time of screening should be referred to local facilities for treatment. If local facilities are not adequate, special arrangements should provide treatment and care.

Even though the balance of opinion is shifting toward provision of ART in the context of prevention research, persistent questions remain unanswered. Who should receive ART—trial participants only, those screened out, family members, or trial staff (sometimes infected with HIV)? Who should be responsible for providing and paying for the ART treatment—and for how long?

In general, most networks and organizations that intend to provide ART for those who seroconvert during a trial are not planning to provide ART for family members, nor for prospective participants who were screened out because they are HIV positive.

When to initiate ART? Many researchers look to WHO guidelines, which recommend that physicians initiate therapy when a patient's CD4 count declines to less than 200 cells per cubic millimeter, or when clinical signs of AIDS become apparent. For those who seroconvert during microbicide trials, ART may not be required until many years after the trial officially ends. This implies a promise that may be easier to make than to keep. For the commitment to be meaningful, researchers must set up sustainable follow-through mechanisms. This means capacity to track, deliver, pay for, monitor, and continue ART for many years after the trials end for a relatively small number of people who may be geographically dispersed.

It should be remembered that most women involved in prevention trials are not infected. Some Consultation participants expressed concern that by focusing too narrowly on ART, donors and advocates may loose sight of the reproductive health care needs of the majority; moreover HIV positive women typically have a plethora of unfulfilled needs beyond access to drugs. A recent survey of services available at HPTN-related trial sites revealed that many lack access to even basic services, such as contraception and nutritional support, prophylaxis, and treatment for other common AIDS-related ailments (see Chapter 7, Box 7).

Other participants in the Consultation countered that ART access has been among the weakest links in AIDS care in developing countries and, as such, warrants special emphasis in discussions of the ethics of clinical trials. Most participants agreed, however, that far more could be done to provide a range of services to women who become infected. This includes reproductive health care, nutrition assistance, treatment of symptoms, and the prevention of opportunistic infections and cancers.[5] A "mapping" of what is and is not included in trial-site benefits packages was suggested as a highly useful next step.

Community consultation

Throughout the discussion, a unifying refrain was to confer with participant populations and communities hosting the research. The benefits package should be determined through a transparent decision-making

[5] One speaker noted, for example, that women are often most bothered by the itchy and unsightly rash and express a desire for treatment for their skin.

BOX 8: A South African Perspective on the ART Debate

Cathy Slack, an ethicist from the University of Kwazulu-Natal, provided a South African perspective on researchers' and trial sponsors' ethical obligation to provide ART to trial participants who seroconvert during prevention trials.[1] The analysis was developed by the HIV/AIDS Vaccine Ethics Group (HAVEG), a working group of the South African AIDS Vaccine Initiative (SAAVI).

Two main arguments have been advanced to support the idea that researchers are ethically obliged to provide ART to participants—first, as compensation for research-related harms, and second, as fair distribution of risks and benefits and reducing inequalities.

Compensation for research-related harms. Although agreeing with the principle that individuals deserve compensation for trial-related injuries, HAVEG argues that this applies only if the test product or the trial itself causes the infection. In microbicide trials, participants become HIV infected *despite* trial-related interventions, not because of them. Others have countered that participation in an HIV prevention trial may cause some people—who mistakenly believe that the candidate product will protect them—to increase their risky behavior; and for this reason, HIV infection during the trial could be viewed as "research related." This position maintains that "behavioral disinhibition" because of the "therapeutic misconception" could be considered a research-related harm.

HAVEG reviewed studies on participants' understanding of the information received about vaccines and their expectations of its effectiveness. They concluded that it is possible, albeit a challenge, to provide participants with a good understanding of the experimental nature of the vaccine, including the fact that it may not offer protection. They also examined the empirical evidence of how risk behavior changes during vaccine and microbicide trials, concluding that risk behavior does not generally increase and is indeed more likely to decline as the trial progresses. Moreover, increase in risky behavior cannot easily be attributed to the trial as distinct from a myriad of other possible causes. While this argument may have some merit at the individual level, HAVEG concluded that it would be hard to justify a "general obligation" for sponsors to provide ART based on the principle of compensation for harm related to the research.

Fair distribution of risks and benefits and reducing inequalities. While providing ART to those who seroconvert would reduce inequalities between industrial and developing countries, providing comprehensive treatment to the few people who seroconvert is not necessarily the best way to redress global health care injustices. One could convincingly argue that this goal would be better served by improving basic health care infrastructure in trial communities. Likewise, providing ART might exacerbate or potentially introduce local inequities—for example, between the people who are already HIV positive at the time of screening and those who seroconvert during the trial, or between those enrolled and their partners or children who may also be HIV positive. (That said, HAVEG also acknowledged that it would be impossible to do any kind of development work without introducing some local inequalities.)

Finally, might the offer of long-term ART be construed as an "undue inducement," motivating prospective participants to take on risks and burdens that they would otherwise reject in order to ensure future access to ART? While acknowledging that some participants might calculate this future benefit as part of a rational decision process, the benefit is uncertain and probably assumes too many steps to

Box 8 Continued on next page

BOX 8: A South African Perspective on the ART Debate *(Continued)*

strongly distort the immediate risk-benefit calculation. On balance, they cautioned against classifying provision of ART as an "undue inducement."

According to HAVEG, these two arguments in themselves do not make the case that sponsors and investigators are obligated to provide ART to infected individuals. However, justice-based arguments do exhort sponsor-investigators to reduce inequalities, despite differences in interpretation of the most "fair" arrangement—for example, whether to aim for comprehensive treatment for a few, or community-level improvements for the many? Wherever researchers and their sponsors have it in their power to reduce suffering of participants in their trials, they should do so to the utmost on the grounds of positive beneficence.

[1] For a more detailed accounting of these arguments, see: Slack C,. et al. Provision of HIV treatment in HIV preventive vaccine trials: a developing country perspective. *Social Science and Medicine*. 2005; 60:1197–1208.

process, not only *involving* the community but prioritizing their expressed wishes. This process understands and accepts that communities do not always express the priorities that researchers and advocates expect.

How a benefits package is viewed and constructed, for example, depends very much on where one happens to be sitting. In the global South, deciding which benefits to include is a process of deciding upon best allocation of scarce resources among many equally valid and compelling needs. For example, HPTN focus group research on health-related priorities found that although women were concerned about diseases such as HIV, they were just as concerned about inadequate hygiene, poor nutrition, and the lack of transportation to obtain care. Other priority needs included lack of staff, drug shortages, and the need to improve the quality of treatment at health services.

In a focus group with HIV positive women, HPTN elicited comments on hypothetical treatment scenarios. The first was that HIV positive women in the trial and their families would be referred for treatment services. The second was that all women in the trial would receive "basic" health care services and HIV positive women and their families would be referred for treatment. The third was "best care," including ART for HIV positive women until the end of the trial and referrals after the conclusion of the trial. Among these choices, the women found the third option most "unfair," because they distrusted long-term promises and rejected the notion of women receiving treatment not available to their partners and families.

Community involvement entails other challenges. If the benefits package is to be developed in consultation with the community, how do researchers figure out who speaks for the community? How do they handle the inequalities between research sponsors and hosts, which may cause a "race to the bottom" in which the urgency of a community's needs causes it to accept research that appears to offer *any* benefit? If the broader community plays a major role in determining the benefits

package, researchers need to take care that participants who are marginalized within those communities are not exploited. When individual and community interests diverge, they must be fairly reconciled.

Even if investigators are able to reach agreement with the trial site communities on what the benefits package should include, many researchers still face formidable bureaucratic hurdles from their donors. For example, as a matter of policy, the US National Institutes of Health (NIH) prohibits the use of clinical research funds after the conclusion of a trial. Without access to funding, researchers can do little to make good on promises to provide services after a trial ends. Thus, advocacy to change donor policy must also be taken on as a high priority.

Clearly, an ad hoc approach to clinical trials is unlikely to work in the face of such complexities. Before the research starts, a well-structured plan must be developed that involves the full gamut of actors and takes the local context into account. Partners are needed who can contribute to solutions. This means investing in local institutions to help create implementation mechanisms for plans such as continuing care when the clinical trials end.

At the very least, researchers should take advantage of existing opportunities to cooperate with ART expansion efforts, such as those being rolled out by the Global Fund and the United States government. Another option is to explore enrolling microbicide trial participants who are HIV positive into a parallel treatment trial. Researchers should work with existing care facilities and NGOs that provide care and treatment for infected individuals, and with networks of women living with HIV/AIDS. Specifically, they should actively seek to apply the GIPA standard (Greater Involvement of People Living with AIDS). Signed by 50 countries, the GIPA standard encourages groups to seek out and engage people living with HIV/AIDS. Finally, they should join the global movement for greater access to treatment.

Indeed, embedding microbicides research into human rights and sexual rights perspectives requires that researchers fight actively for all women's rights to dignity, respect, and well being. This requires advocacy to expand services to meet the diverse needs of women in the broader community—for example, services for unwanted pregnancy, violence, and STDs.