HIV Prevention Trials Network

QUESTIONS AND ANSWERS

The HPTN 052 Study:

Preventing Sexual Transmission of HIV with Anti-HIV Drugs

1. What is the HPTN 052 study?

The HPTN 052 study is a Phase III randomized clinical trial with the primary objective of evaluating whether antiretroviral therapy (ART), which is a combination of medicines currently licensed to treat HIV infection, can prevent the sexual transmission of HIV among couples in which one partner is HIV-infected and the other is not (serodiscordant couples). Additionally, the study was designed to evaluate the optimal time to begin ART in order to reduce illness and death among people infected with HIV/AIDS.

2. Who funded and conducted the HPTN 052 study and when did it begin?

The study was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). Led by protocol chair Myron Cohen, M.D., director of the Institute for Global Health and Infectious Diseases at the University of North Carolina at Chapel Hill, the study was conducted by the HIV Prevention Trials Network (HPTN), which is largely funded by NIAID with additional funding from the National Institute on Drug Abuse and the National Institute of Mental Health, both part of the NIH. Additional support was provided by the NIAID-funded AIDS Clinical Trials Group.

The study began in April 2005. Enrollment ended in May 2010.

3. How many participants were involved in the study, and where was the study conducted?

A total of 1,763 serodiscordant couples participated in the study. Each participant was at least 18 years of age (median age of 33). The vast majority of the couples (97 percent) were heterosexual. At the time of enrollment, the HIV-infected partners (890 men, 873 women) had CD4+ T-cell counts, a key measure of immune system health, between 350 and 550 cells per cubic millimeter (mm^3) within 60 days of entering the study. The median CD4 count at study entry was 436 cells/mm^3. The HIV-uninfected partners tested negative for the virus within 14 days of entering the study.

The study took place at 13 sites in Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, the United States and Zimbabwe.

4. What was the study's design?

Participating couples were randomly assigned to one of two treatment arms. In the first group, the HIV-infected partners immediately began taking a combination of three antiretroviral therapy (ART) drugs.

In the second group, the HIV-infected partners delayed taking ART until their CD4 counts fell below 250 cells/mm^3, or an AIDS-related illness as defined by World Health Organization guidelines occurred. All participants in both groups received counseling on safe sex practices, free condoms, treatment for sexually transmitted infections, frequent HIV testing and evaluation and treatment for any complications related to HIV infection.

5. Which antiretroviral therapy (ART) drugs were used in the study?

HPTN 052 participants were given a combination three- or four-drug regimen using the following 11 HIV drugs:

- Atazanavir (300 mg once daily)
- Didanosine (400 mg once daily)
- Efavirenz (600 mg once daily)
- Emtricitabine/tenofovir disoproxil fumarate (200 mg emtricitabine/300 mg tenofovir disoproxil fumarate once daily)
- Lamivudine (300 mg once daily)
- Lopinavir/ritonavir 800/200 mg daily (Qday) or lopinavir/ritonavir 400/100 mg twice daily (BID)
- Nevirapine (200 mg taken once daily for 14 days followed by 200 mg taken twice daily)
- Ritonavir (100 mg once daily, used only to boost atazanavir)
- Stavudine (weight-dependent dosage)
- Tenofovir disoproxil fumarate (300 mg once daily)
- Zidovudine/lamivudine (150 mg lamivudine/300 mg zidovudine taken orally twice daily)

The study drugs were donated by Abbott Laboratories; Boehringer Ingelheim Pharmaceuticals, Inc.; Bristol-Myers Squibb; Gilead Sciences; GlaxoSmithKline and Merck & Co., Inc.

6. What is a Data and Safety Monitoring Board, and how did it monitor this study?

A Data and Safety Monitoring Board (DSMB) is an independent committee composed of clinical research experts, statisticians, ethicists, and community representatives that provides additional oversight of a clinical study. The DSMB regularly reviews data while a clinical trial is under way to ensure the safety of the participants and that any benefits shown in the study are quickly made available to all participants. A DSMB may recommend that a clinical trial, or part of a trial, be stopped or modified if there are safety concerns or if the trial objectives have been achieved or are unlikely to be achieved. A DSMB looks at analyses that are not available to the investigators. Restricting certain information to the DSMB while the trial is ongoing helps to maintain the integrity of the study.

The DSMB for the HPTN 052 study met at regular intervals throughout the course of the trial to review the study data. On April 28, 2011, the DSMB met for a scheduled interim review of the study's safety and effectiveness data.

7. What were the DSMB's findings related to HIV transmission?

The DSMB found a total of 39 cases of HIV infection among the previously uninfected partners. Of those, 28 were linked through genetic testing to the HIV-infected partner as the source of infection. Seven infections were not linked to the HIV-infected partner, and four infections were undergoing analysis.

Of the 28 cases of linked HIV infection that occurred, 27 infections were among the 877 couples in which the HIV-infected partner delayed ART. Only one case of HIV infection occurred among the 886 couples in which the HIV-infected partner began immediate ART. Restated, this means that earlier initiation of ART led to a 96 percent reduction in HIV transmission to the HIV-uninfected partner. This result was statistically significant ($P \leq 0.0001$).

Based on this finding, the DSMB recommended that the study participants be notified of the results.

8. What were the DSMB's findings related to potential benefits associated with early ART use?

There were 105 morbidity and mortality events. There was a total of 65 events in the delayed treatment arm and 40 in the immediate treatment arm. The DSMB found 17 cases of extrapulmonary tuberculosis among HIV-infected participants in the delayed treatment group compared with three cases in the immediate treatment arm. This was a statistically significant finding ($P=0.0013$). There were 23 deaths during the study: 10 in the immediate treatment group and 13 in the delayed treatment group, a difference that did not reach statistical significance. Overall, there was a trend toward benefit for the HIV-infected participants who started ART immediately, but it did not reach the 20 percent difference between study arms required for statistical significance.

9. What do these findings mean for the study participants?

The study participants are being informed of the results. ART is being offered to all consenting HIV-infected participants in the delayed treatment arm. The study investigators will continue to follow the study participants for at least one year.

Individuals who became HIV-infected during the course of the study were referred to local services for appropriate medical care and treatment.

10. One of the HPTN 052 study arms involved delaying ART until CD4 counts reached or fell below 250 cells per cubic millimeter. However, in 2009, the World Health Organization (WHO) revised its guidelines for when to initiate ART recommending treatment in HIV-infected individuals with CD4 counts less than 350 cells/mm³. Was it unethical to continue the study arm based on the WHO revisions?

When the study began enrolling in April 2005, the protocol and the in-country guidelines of the participating sites were consistent with the WHO treatment guidelines (November 2003) that recommended that anyone with advanced clinical HIV disease or those with CD4+ T-cell counts less than 200 cells/mm³ begin ART. The WHO guidelines were revised over time, recommending first that ART be considered between 200 and 350 cells/mm³ and initiated before 200 cells/mm³ (January 2006), and then to initiate ART in all patients who have a CD4 cell count of less than 350 cells/mm³, irrespective of clinical symptoms (November 2009). In response to the first revision, most countries quickly adopted the new guidelines, and the study team changed the protocol such that the criteria for initiating ART in the delayed treatment arm went from less than 200 cells/mm³ to between 200 and 250 cells/mm³ and raised the entry criteria for CD4 cell count from 300 to 500 cells/mm³ to 350 to 550 cells/mm³ to maintain the integrity of the study design. However, the second revision was not readily adopted by all of the countries participating in the study, primarily due to a lack of drug supply.

The study team, NIAID, and the DSMB carefully considered the same data that led to the second revision of the WHO guidelines. The DSMB concluded that no change in the study was necessary based on existing HPTN 052 data and taking into consideration the safety of the participants. Nevertheless, the study team and NIAID determined that all participants should be notified of the change in the WHO guidelines and any corresponding changes in country guidelines and reminded that they are free to leave the study at any time or to start ART outside of the study, according to the local standard of care. This action was approved by all of the institutional review boards and ethics committees overseeing the study.

11. What additional results have become available since the DSMB review?

At the time of the April 28, 2011 DSMB review, 28 linked transmission events had been identified. This included only one event where transmission occurred after the HIV-infected partner began ART. This event was in the immediate treatment arm. Subsequent detailed analysis indicated that this transmission most likely occurred within days of the couple's enrollment in the study, before viral suppression could be achieved in the HIV-infected partner. Results obtained after the DSMB meeting also identified one additional linked transmission event that involved an HIV-infected participant in the delayed treatment arm; that event occurred shortly after the HIV-infected participant started ART. Because the additional linked event was in the delayed treatment arm, it further strengthened the association between immediate ART and HIV prevention. Additional analyses performed after the DSMB meeting also showed that the probability of unlinked HIV transmission was greater in uninfected partners who reported having more than one sexual partner in the three months before they were diagnosed with HIV infection.

Other analyses performed after the DSMB meeting revealed regional differences in disease progression, as well as regional differences in HIV transmission, with a disproportionate percentage of transmissions occurring in Africa. HIV-infected participants in the delayed treatment arm also had lower CD4 cell counts one year after beginning ART compared to participants in the immediate treatment arm. This suggests that even a modest delay in ART initiation may compromise the clinical response to treatment.

12. What are the implications of this study for HIV/AIDS treatment and prevention?

In light of the results of HPTN 052, the World Health Organization (WHO) is reviewing its recommendations regarding testing and counseling and ART for treatment and prevention in couples with only one HIV-infected partner.

The HIV prevention result seen in this study is also a definitive test of concept for the use of ART for prevention of sexual transmission. This strengthens approaches to HIV prevention that promote community-wide HIV testing with immediate linkage to care and treatment for those testing positive.

These results do not indicate the duration of ART's protective benefit to the uninfected partner over time. Results also do not indicate whether a delay in ART has long-term adverse clinical effects, such as cardiovascular complications or cancer. Plans are under way to investigate both of these questions.

Although all participants received information, counseling, and free condoms, unlinked transmissions occurred, indicating a continued need for behavior-change prevention efforts.

13. What is the current state of the HIV/AIDS epidemic?

HIV/AIDS continues to be a significant global public health problem. Worldwide, 2.6 million people became newly infected with HIV in 2009 alone, and 1.8 million people died of AIDS-related disease, bringing the total number of AIDS deaths to about 30 million since the beginning of the epidemic. Here in the United States, more than 56,000 people become infected with HIV each year. In all, about 600,000 people with AIDS in the U.S. have died.

14. About the HIV Prevention Trials Network

The HIV Prevention Trials Network (HPTN) is a global clinical trials network that develops and tests interventions designed to prevent HIV acquisition and transmission (www.hptn.org). Funded by the NIAID, HPTN is a collaboration among leading scientists, investigators, and advisors from major international and U.S. research and government institutions. With ongoing clinical trials in more than a dozen countries, HPTN studies focus on populations and geographical regions that bear a disproportionate burden of infection.

HPTN's vision for HIV prevention is to develop and evaluate interventions that help stop the spread of HIV at every point on the continuum of acquisition and transmission — thus radically inhibiting the spread of the disease.

For example, recognizing that knowledge of one's HIV status is the first step in prevention, HPTN has studies under way to evaluate the expansion of HIV testing, including the use of mobile units to offer testing and counseling to those living in remote rural areas of Africa and Thailand (HPTN 043, also known as Project ACCEPT), as well as the promotion of community-wide testing in Washington, D.C., and the Bronx, NY (HPTN 065, also called Testing and Linkage to Care Plus or TLC-Plus). In addition to expanded HIV-testing, TLC-Plus is evaluating methods to ensure that those who test positive are immediately linked to appropriate counseling, care and treatment. This "test-and-treat" strategy takes on new urgency as HPTN 052 has shown that early initiation of ART reduces transmission within serodiscordant couples. TLC-Plus is also evaluating methods for incentivizing HIV-infected individuals taking ART to remain adherent and achieve viral suppression — both for their own benefit and, now, as viral suppression may help reduce transmission. Other HPTN research includes the prophylactic use of HIV drugs to prevent acquisition in men who have sex with men and in heterosexual women, testing financial incentives as a way to keep at-risk girls in school, and treatment of injection drug abuse to prevent HIV transmission.

To fully realize the public health potential of advances in treatment and prevention, HPTN is pursuing research that evaluates combinations of the best available evidence-based tools for HIV prevention, their appropriateness for different epidemic settings, and their impact at a population level. An upcoming study, conducted in collaboration with the Office of the United States Global AIDS Coordinator and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), will evaluate the impact of a combination prevention strategy on HIV incidence and assess the population-level coverage of the proposed combination. All HPTN studies are conducted in close partnership with the community as well as national and local health authorities.