Antiretroviral Therapy for the Prevention of HIV-1 Transmission


BACKGROUND
An interim analysis of data from the HIV Prevention Trials Network (HPTN) 052 trial showed that antiretroviral therapy (ART) prevented more than 96% of genetically linked infections caused by human immunodeficiency virus type 1 (HIV-1) in serodiscordant couples. ART was then offered to all patients with HIV-1 infection (index participants). The study included more than 5 years of follow-up to assess the durability of such therapy for the prevention of HIV-1 transmission.

METHODS
We randomly assigned 1763 index participants to receive either early or delayed ART. In the early-ART group, 886 participants started therapy at enrollment (CD4+ count, 350 to 550 cells per cubic millimeter). In the delayed-ART group, 877 participants started therapy after two consecutive CD4+ counts fell below 250 cells per cubic millimeter or if an illness indicative of the acquired immunodeficiency syndrome (i.e., an AIDS-defining illness) developed. The primary study end point was the diagnosis of genetically linked HIV-1 infection in the previously HIV-1–negative partner in an intention-to-treat analysis.

RESULTS
Index participants were followed for 10,031 person-years; partners were followed for 8509 person-years. Among partners, 78 HIV-1 infections were observed during the trial (annual incidence, 0.9%; 95% confidence interval [CI], 0.7 to 1.1). Viral-linkage status was determined for 72 (92%) of the partner infections. Of these infections, 46 were linked (3 in the early-ART group and 43 in the delayed-ART group; incidence, 0.5%; 95% CI, 0.4 to 0.7) and 26 were unlinked (14 in the early-ART group and 12 in the delayed-ART group; incidence, 0.3%; 95% CI, 0.2 to 0.4). Early ART was associated with a 93% lower risk of linked partner infection than was delayed ART (hazard ratio, 0.07; 95% CI, 0.02 to 0.22). No linked infections were observed when HIV-1 infection was stably suppressed by ART in the index participant.

CONCLUSIONS
The early initiation of ART led to a sustained decrease in genetically linked HIV-1 infections in sexual partners. (Funded by the National Institute of Allergy and Infectious Diseases; HPTN 052 ClinicalTrials.gov number, NCT00074581.)
ADVANCES IN THE TREATMENT AND CARE of patients with human immunodeficiency virus type 1 (HIV-1) infection have led to dramatic reductions in the morbidity and mortality associated with this disease. However, despite intensive public health initiatives aimed at HIV-1 prevention, more than 2 million new HIV-1 infections were reported in 2014 worldwide.

The global HIV-1 epidemic is primarily driven by sexual transmission. Potent, durable HIV-1 prevention strategies are required to reduce the risk of viral transmission from infected persons to their sexual partners. Observational studies involving serodiscordant couples have suggested that antiretroviral therapy (ART) in persons with HIV-1 infection reduces the risk of sexual transmission of the virus. The multinational, randomized, controlled HIV Prevention Trials Network (HPTN) 052 trial was designed to determine the effect of ART on the transmission of HIV-1 from infected persons to their sexual partners.

The HPTN 052 trial enrolled 1763 serodiscordant couples at 13 sites in nine countries. Index participants (i.e., those with HIV-1 infection) had CD4+ counts of 350 to 550 cells per cubic millimeter. Couples were randomly assigned to two study groups. In the early-ART group, index participants initiated ART at the time of enrollment. In the delayed-ART group, index participants initiated ART when two consecutive CD4+ counts fell below 250 cells per cubic millimeter or they had an illness indicative of the acquired immunodeficiency syndrome (i.e., an AIDS-defining illness).

In an interim analysis of study data that was performed in May 2011 after a median follow-up of 1.7 years, investigators found that early ART was associated with a 96% lower risk of index-to-partner, genetically linked HIV-1 infections than was delayed ART. The interim analysis also showed that early ART provided health benefits to the index participants. The data and safety monitoring board requested immediate release of those results. Accordingly, after May 2011, all index participants who were not already receiving ART were offered ART, regardless of the CD4+ count. The trial continued as prespecified through May 2015 to assess the durability of the effect of ART on HIV-1 transmission. This report presents the final results of the HPTN 052 trial.

STUDY DESIGN

The HPTN 052 trial enrolled participants in Malawi, Zimbabwe, South Africa, Botswana, Kenya, Thailand, India, Brazil, and the United States, with pilot enrollment from April 2005 through May 2007 and full enrollment from June 2007 through May 2010. Detailed descriptions of the study and interim study results have been published previously. Data analysis was conducted in accordance with a prespecified analysis plan, as reported previously.

At enrollment, index participants reported no previous use of antiretroviral drugs, with the exception of short-term use for the prevention of mother-to-child transmission. Couples were randomly assigned to one of the two above-mentioned study groups. Prophylaxis with isoniazid or trimethoprim–sulfamethoxazole was provided to index participants according to local guidelines. Follow-up visits were conducted monthly for 3 months after enrollment and then quarterly.

CLINICAL AND LABORATORY EVALUATIONS

At the time of enrollment and at follow-up visits, index participants underwent clinical and laboratory evaluations and received condoms and counseling for risk reduction and medication adherence. Their partners who were free of HIV-1 infection were followed on the same visit schedule and were tested for HIV-1 at each study visit. Partner infections were confirmed at the HPTN Laboratory Center at Johns Hopkins University School of Medicine. After public release of the interim results in May 2011, all index participants were offered ART.

ASSESSMENT OF GENETIC LINKAGE

The genetic linkage of partner infections was assessed by means of phylogenetic analysis of HIV-1 polymerase (pol) region sequences, including sequences from index–partner pairs, sequences from unrelated index participants, and reference sequences. Probability of linkage was also assessed by means of Bayesian methods to compare genetic distances between sequences from index–partner pairs and unrelated participants. Selected cases were further analyzed by phylogenetic analysis of HIV-1 envelope (env) region sequences obtained with the use of next-
generation sequencing. Additional testing was performed to assess the timing of HIV-1 infection in selected cases. These methods have been described previously\textsuperscript{9,10} and are summarized in the Supplementary Appendix, which is available with the full text of this article at NEJM.org.

**STUDY OVERSIGHT**

The study was funded by the National Institute of Allergy and Infectious Diseases, which assumed all sponsor responsibilities through an investigational new-drug application with the Food and Drug Administration. The study protocol, available at NEJM.org, was approved by the institutional review board or ethics committee at each study site, as well as by other local regulatory bodies, as appropriate, and by the institutional review board at the U.S. Centers for Disease Control and Prevention (CDC) for the CDC-affiliated site in Kenya. All study participants provided written informed consent. The antiretroviral drugs that were used in the study were donated by Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV Healthcare, and Merck. The drug manufacturers were not involved in the design or management of the study or in the analysis or reporting of the data. The authors vouch for the completeness and accuracy of the data and the analysis and for the fidelity of this report to the protocol.

**STATISTICAL ANALYSIS**

A detailed description of the statistical considerations and the HPTN 052 statistical analysis plan have been published previously.\textsuperscript{7} The statistical analysis was performed on an intention-to-treat basis of the index participant’s randomization assignment to assess the primary end point of incident partner infections during the study follow-up. If an HIV-1–negative partner was lost to follow-up before the primary end point was reached, the index partner remained in the study. In some cases, index participants found new partners who were willing to be enrolled. Such replacement partners were included in the statistical analysis as if they had been the original partners. Replacement partners were enrolled throughout the study, both before and after the release of the interim study results. We used the Kaplan–Meier method to calculate cumulative event probabilities; person-year analyses were used to determine HIV-1 incidence rates before and after the public release of the interim study results. We used Cox regression models to estimate relative risk, as expressed by means of hazard ratios for the treatment effect of early ART versus delayed ART, with or without key baseline covariates, after adjustments, along with the 95% confidence intervals.

**RESULTS**

**TRIAL PARTICIPANTS**

The HPTN 052 trial enrolled 1763 serodiscordant couples (886 in the early-ART group and 877 in the delayed-ART group) (Fig. 1). The median follow-up time was 5.5 years (range, 0.0 to 9.9) for the early-ART group and 5.5 years (range, 0.1 to 9.9) for the delayed-ART group. The interim study results were released to the public on May 12, 2011. At that time, 1702 (97%) of the index participants remained in the study, along with 1563 (89%) of the partners, including 3 partners who were retained after the index participant discontinued involvement in the study. Rates of retention were similar in the two study groups (Fig. S2 in the Supplementary Appendix). By the end of the study (May 2015), 1536 (87%) of the index participants remained in the study, with 10,031 person-years of follow-up; 1165 (66%) of the couples remained in the study, with similar distribution in the two study groups (Fig. S2 in the Supplementary Appendix). Partners were followed for 8509 person-years. Rates of annual visit attendance among the partners were similar in the two study groups; the reasons for early discontinuations among the partners are shown in Figure 1.

Among male partners, there was no significant between-group difference in the rate of circumcision between the early-ART group and the late-ART group during the course of the study (22.3% and 18.3%, respectively; \textit{P}=0.13). The rates of sexually transmitted infections that were detected among the index participants were also similar in the two study groups (Table S1 in the Supplementary Appendix).
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Figure 1. Study Randomization and Outcomes.

Shown are data on the randomization of couples, enrollment of partners, partner visit attendance, and reasons for early discontinuation of partners in the study. Thirty additional partners (17 in the early-ART group and 13 in the delayed-ART group) were enrolled throughout the course of the study to replace partners who discontinued their participation in the study before reaching a primary study end point. The four partners who were found to have HIV-1 infection at study enrollment were excluded from the analysis. Visit attendance is shown for annual visits only; actual study visits occurred at least quarterly. The data for annual visit attendance are presented as the number of partners (nonindex participants) who were retained per the number who were expected at each year-end visit. The number retained refers to the number of partners who completed visits or reached a study end point (i.e., death of the index participant or the diagnosis of HIV-1 infection in the partner). The expected number refers to the number of partners who did not discontinue participation in the study because of death or the termination of the relationship with the index participant before the end of the allowable visit period.
By May 2011, all index participants in the early-ART group and 26% of those in the delayed-ART group had initiated ART. After the release of the interim study results, ART was offered to all index participants in the delayed-ART group regardless of CD4+ count. One year later, 83% of index participants who continued to be followed in the delayed-ART group were receiving ART (Fig. S3 in the Supplementary Appendix). Index participants in the delayed-ART group who chose not to start ART were asked about their decision; most commonly, these participants indicated that they deferred ART because their CD4+ count was too high or because they believed that they were too healthy to begin treatment and risk side effects. By the end of the study, 96% of participants who remained in follow-up in the delayed-ART group had initiated ART (Fig. S3 in the Supplementary Appendix).

Transmission of HIV-1 Infection to Partners

We documented HIV-1 infections in 78 partners during the course of the trial, with an incidence of 0.9% (95% confidence interval [CI], 0.7 to 1.1) in the two study groups combined. These infections included 19 in the early-ART group and 59 in the delayed-ART group. The primary end point of the trial was the incidence of genetically linked partner infections, which were identified with the use of phylogenetic and statistical methods. Of the 78 infections, viral linkage status was determined in 72 (92%), with 6 analytic failures (the viral load was too low for amplification or amplification failed) (Table 1, and Fig. S1 in the Supplementary Appendix).

Of the 78 infections, viral-linkage status was determined, 26 (36%) — 14 in the early-ART group and 12 in the delayed-ART group — were found to be unlinked, which indicates that the index participant was most likely not the source of the partner's infection (incidence in the two study groups combined, 0.3%; 95% CI, 0.2 to 0.4). The remaining 46 infections were linked (3 in the early-ART group and 43 in the delayed-ART group). The median CD4+ count of the index participants at the visit before the diagnosis of infection in their partners was 390 cells per cubic millimeter (range, 223 to 748) for linked partner infections and 541 (range, 272 to 1312) for unlinked partner infections.

Eight linked partner HIV-1 infections were
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In four cases, the partner was diagnosed with HIV-1 infection less than 90 days after the index participant started ART. In these cases, further analysis suggested that all four of these infections probably occurred before the infection was virally suppressed in the index participant (Table 2). In the other four cases, partner infection occurred after ART failed in the index participant.10

### Table 2. Characteristics of Eight Linked Partner Infections Diagnosed after the Index Participant Initiated ART.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at ART Initiation</th>
<th>Index Viral Suppression 6 Mo after ART Initiation†</th>
<th>No. of Days before or after ART Initiation‡</th>
<th>No. of Days between Last Measure of Index Viral Load and Estimated Infection Date</th>
<th>Last Index Viral Load before Estimated Infection Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>43</td>
<td>Yes</td>
<td>NA −35</td>
<td>35 −5 (−18 to 10)</td>
<td>34 278,398</td>
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<td>B</td>
<td>24</td>
<td>Yes</td>
<td>NA −1</td>
<td>84 0 (−32 to 19)</td>
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<tr>
<td>C</td>
<td>50</td>
<td>Yes</td>
<td>NA 0</td>
<td>59 5 (−4 to 22)</td>
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<tr>
<td>D</td>
<td>34</td>
<td>No</td>
<td>261 −42</td>
<td>49 4</td>
<td>4 &gt;750,000</td>
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<tr>
<td>E</td>
<td>25</td>
<td>No</td>
<td>208 1019</td>
<td>1106 1062</td>
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<tr>
<td>F</td>
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<td>1716 1667</td>
<td>50 617</td>
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<tr>
<td>G</td>
<td>46</td>
<td>No</td>
<td>362 2095</td>
<td>2228 2162</td>
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<td>H</td>
<td>28</td>
<td>No</td>
<td>891 860</td>
<td>1419 1140</td>
<td>ND ND</td>
</tr>
</tbody>
</table>

* HIV-1 infection was diagnosed in eight partners after the infected index participant initiated ART. NA denotes not applicable, and ND not determined.
† "Yes" indicates that the index participant had viral suppression (viral load, <400 copies per milliliter) 6 months after ART initiation.
‡ The number of days between ART initiation (day 0) and other events is shown; negative numbers indicate days before ART initiation; positive numbers indicate days after ART initiation.
§ The initial ART regimen failed in five of the eight index participants. ART failure was defined as a viral load of more than 1000 copies per milliliter on two consecutive visits after receiving ART for more than 24 weeks.
¶ In cases A, B, and C, the index participant had viral suppression at the time that HIV-1 infection was diagnosed in the partner. In those cases, the infection date was estimated with the use of Bayesian evolutionary analysis by sampling trees (BEAST) and other molecular and serologic methods and included 95% confidence intervals.10 In cases D through H, the infection date was estimated as the midpoint between the partner’s last negative test and first positive test for HIV-1.
‖ In case H, the partner was lost to follow-up for an extended period. The partner’s last negative HIV-1 test was 860 days after the initiation of ART in the index participant, and the partner’s first positive HIV-1 test was on day 1419. Four measurements of viral load were obtained for the index participant between day 860 and day 1419 (10,457 copies per milliliter on day 891, 15,944 copies on day 955, <400 copies on day 980, and <400 copies on day 1008).

Risk of Partner HIV-1 Infection

In an intention-to-treat analysis to compare the number of linked partner infections in the two study groups (the primary study end point), early ART was associated with a 97% lower risk than was delayed ART as of May 2011 and a 93% lower risk during the entire study. This analysis also showed an estimated 90% lower risk of all partner infections (regardless of linkage status) as of May 2011 and a 69% lower risk in all partner infections during the entire study in the early-ART group (Table 1).

In the Kaplan–Meier analysis, there was an immediate and sustained reduction in linked partner infections after the initiation of ART in the index participant (Fig. 2). The incidence of HIV-1 infection in the delayed-ART group was 36 per 1731.1 person-years from the beginning of the trial through May 12, 2011, and then fell to 7 per 2453.6 person-years after May 12, 2011, to the end of the trial (Table 1). Detailed information on the incidence of partner infections during each year of study follow-up is provided in Table S2 in the Supplementary Appendix.
**Figure 2.** Kaplan–Meier Estimates of the Risk of HIV-1 Infection among Partners of Index Participants.

Shown are the cumulative probabilities of all partner infections (Panel A) and genetically linked partner infections (Panel B) during study follow-up. The insets show the same data on an expanded y axis.

**ASSOCIATION BETWEEN INFECTION AND STUDY VARIABLES**

Univariate and multivariate intention-to-treat analyses were performed to examine the association between the study group and other factors with all partner infections and with linked partner infections (Table 3). In these analyses, the hazard ratios for the association between the study group and partner infection were nearly identical in both univariate and multivariate models. The analysis also showed that an increased CD4+ count among the index participants at baseline was associated with both linked infections and all infections among partners; in addition, an increased baseline index viral load was associated with linked partner infections. In the delayed-ART group, an increased CD4+ count at baseline was associated with a longer time until the initiation of ART (hazard ratio, 0.90; 95% CI, 0.85 to 0.96; P = 0.002), whereas an increased viral load at baseline was associated with a shorter time until the initiation of ART (hazard ratio, 1.31; 95% CI, 1.19 to 1.44; P < 0.001). Less frequent condom use (<100%, by self-report by either partner) was associated with an increased risk of both linked infections and all infections among partners.

**DISCUSSION**

Over the course of our study involving HIV-1 serodiscordant couples, there was a 93% lower risk of genetically linked HIV-1 infection among partners in the early-ART group than in the delayed-ART group in the intention-to-treat analysis. Between May 2011 and May 2015, there were only two cases of linked HIV-1 infection per 2573 person-years of follow-up. After May 2011, couples in the delayed-ART group also derived a benefit from the evolving initiation of ART. However, even during the latter part of the study, the risk of linked HIV-1 infection among partners remained higher in the delayed-ART group than in the early-ART group (Table 1 and Fig. 2, and Table S2 in the Supplementary Appendix).

Over the course of the study, eight genetically linked partner infections were observed after the index participant had initiated ART (three in the early-ART group and five in the delayed-ART group). In all eight cases, the data indicated that the index participant was most likely viremic at the time of HIV-1 transmission, although it was not possible to measure the viral load at the time of the transmission event. The relationship between viremia and HIV transmission that we observed in this study emphasizes the importance of counseling with respect to the potential for HIV-1 transmission before viral suppression is achieved, of close monitoring of the viral load during treatment, and of responding quickly in cases of ART failure.11 Previous studies have reported the transmission of HIV-1 by only one participant in whom the infection was stably suppressed during receipt of ART.12,13 However, we did not document any such transmission events in this study.
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After the release of the interim study results, 17% of the index participants in the delayed-ART group initially chose not to start ART, even though they were informed of the personal and public health benefits of such therapy (Fig. S3 in the Supplementary Appendix). This finding probably reflects the relative good health of the participants with HIV-1 infection and the former recommendations of worldwide guidelines that ART was not required for the treatment of infection until there was a decrease in the CD4+ count or a deterioration in health.14,15 We hope that the newly emphasized importance of early initiation of ART16-18 will encourage patients with HIV-1 infection to start such therapy without delay.

Unlinked partner infections (i.e., cases in which the partner was most likely infected by someone other than the enrolled index participant) were observed in the two study groups and represented approximately 30% of partner infections throughout the study; a similar frequency of unlinked infections was reported in another study involving serodiscordant couples.19 We observed one unlinked partner infection for every 300 person-years of follow-up. The prevention of unlinked HIV-1 infections will require the use of combination prevention strategies that target the broader community.20 Data on the frequency of linked and unlinked partner infections may be helpful for advising HIV-1 serodiscordant couples21,22 and clarifying the assumptions that are used in mathematical modeling and cost-effectiveness exercises.23

As expected, index participants who had increased viral loads at baseline were significantly more likely to transmit HIV-1 to their sexual partners.24 In contrast, self-reported condom use by either partner was associated with a reduced risk of HIV-1 acquisition. An increased baseline CD4+ count among index participants in the delayed-ART group was associated with a greater probability of linked partner infections, which may reflect a longer delay in the initiation of ART and thus more opportunity for HIV-1 transmission.

Previous observational studies involving participants with HIV-1 infection have shown lower rates of viral transmission both among heterosexual couples3,4 and among men who have sex with men25 when the infected person was receiving ART. The final results of the HPTN 052 trial are consistent with those findings and support the importance of viral suppression for HIV-1 prevention. Recent reports have shown that very early initiation of ART can preserve immune function and reduce complications of HIV-1 infection.16-18 In our study, the early initiation of ART also provided health benefits to the participants receiving treatment.8

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Partner Infections</th>
<th>Linked Partner Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate Analysis</td>
<td>Multivariate Analysis</td>
</tr>
<tr>
<td>Early vs. delayed ART with follow-up through May 2015</td>
<td>0.32 (0.19–0.54)</td>
<td>0.34 (0.20–0.57)</td>
</tr>
<tr>
<td>Baseline CD4+ count per 100 increment</td>
<td>1.19 (1.02–1.38)</td>
<td>1.21 (1.04–1.41)</td>
</tr>
<tr>
<td>Baseline viral load per unit log10 increment</td>
<td>1.08 (0.82–1.42)</td>
<td>1.18 (0.89–1.56)</td>
</tr>
<tr>
<td>Male sex vs. female sex of index participant</td>
<td>0.85 (0.54–1.35)</td>
<td>0.86 (0.54–1.39)</td>
</tr>
<tr>
<td>Baseline condom use of 100% vs. &lt;100% by either partner</td>
<td>0.34 (0.19–0.64)</td>
<td>0.33 (0.18–0.61)</td>
</tr>
</tbody>
</table>

* Hazard ratios were calculated by means of both univariate and multivariate Cox regression analysis, stratified according to study site. The results are similar to those calculated by means of unstratified Cox regression analysis (not shown). All the associations were significant (P<0.05) except for baseline viral load in the analysis of all partner infections and male sex versus female sex of the index participant in the analyses of all partner infections and linked partner infections.
for universal HIV-1 testing and the provision of ART to all persons with HIV-1 infection, regardless of CD4+ count. Clinical trials are now evaluating the extent to which the provision of early therapy can reduce the population-level incidence of HIV-1 infection. The most effective implementation of ART for HIV-1 prevention on a population level will require intensive HIV-1 testing programs and reliable and sustained programs for immediate and universal access to HIV-1 therapy.

In conclusion, the final results of the HPTN 052 study show that successful treatment of HIV-1 is a highly effective tool for the prevention of sexual transmission of the virus. These findings support the results of observational studies and controlled clinical trials showing the personal and public health benefits of the earliest possible initiation of HIV-1 treatment.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the CDC.


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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX


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