

## ORIGINAL ARTICLE

# Early versus Standard Antiretroviral Therapy for HIV-Infected Adults in Haiti

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## ABSTRACT

**BACKGROUND**

For adults with human immunodeficiency virus (HIV) infection who have CD4+ T-cell counts that are greater than 200 and less than 350 per cubic millimeter and who live in areas with limited resources, the optimal time to initiate antiretroviral therapy remains uncertain.

**METHODS**

We conducted a randomized, open-label trial of early initiation of antiretroviral therapy, as compared with the standard timing for initiation of therapy, among HIV-infected adults in Haiti who had a confirmed CD4+ T-cell count that was greater than 200 and less than 350 per cubic millimeter at baseline and no history of an acquired immunodeficiency syndrome (AIDS) illness. The primary study end point was survival. The early-treatment group began taking zidovudine, lamivudine, and efavirenz therapy within 2 weeks after enrollment. The standard-treatment group started the same regimen of antiretroviral therapy when their CD4+ T-cell count fell to 200 per cubic millimeter or less or when clinical AIDS developed. Participants in both groups underwent monthly follow-up assessments and received isoniazid and trimethoprim-sulfamethoxazole prophylaxis with nutritional support.

**RESULTS**

Between 2005 and 2008, a total of 816 participants — 408 per group — were enrolled and were followed for a median of 21 months. The CD4+ T-cell count at enrollment was approximately 280 per cubic millimeter in both groups. There were 23 deaths in the standard-treatment group, as compared with 6 in the early-treatment group (hazard ratio with standard treatment, 4.0; 95% confidence interval [CI], 1.6 to 9.8;  $P=0.001$ ). There were 36 incident cases of tuberculosis in the standard-treatment group, as compared with 18 in the early-treatment group (hazard ratio, 2.0; 95% CI, 1.2 to 3.6;  $P=0.01$ ).

**CONCLUSIONS**

Early initiation of antiretroviral therapy decreased the rates of death and incident tuberculosis. Access to antiretroviral therapy should be expanded to include all HIV-infected adults who have CD4+ T-cell counts of less than 350 per cubic millimeter, including those who live in areas with limited resources. (ClinicalTrials.gov number, NCT00120510.)

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**T**HE OPTIMAL TIME TO INITIATE ANTIRETROVIRAL therapy in adults who are infected with human immunodeficiency virus (HIV) remains uncertain. There have been no randomized trials to determine the optimal time to start antiretroviral therapy in adults who have CD4+ T-cell counts that are greater than 200 and less than 350 per cubic millimeter. Furthermore, there are few data on the optimal time to start antiretroviral therapy in persons who live in locations with limited resources, where high rates of tuberculosis, malnutrition, and coinfection with tropical diseases may alter the natural history of HIV disease and the optimal time to initiate therapy. Therefore, international guidelines differ on when to start antiretroviral therapy.<sup>1-6</sup>

In Haiti, following World Health Organization (WHO) guidelines, the first-line regimen of antiretroviral therapy, which consists of zidovudine, lamivudine, and efavirenz, is initiated when the CD4+ T-cell count in a patient with HIV type 1 (HIV-1) infection is 200 per cubic millimeter or less or when clinical acquired immunodeficiency syndrome (AIDS) develops.<sup>1,2</sup> Among patients who are treated according to this standard strategy for the initiation of antiretroviral therapy, approximately 80% are alive at 5 years.<sup>7,8</sup> We conducted a randomized clinical trial in Haiti to determine whether early initiation of antiretroviral therapy, as compared with the standard timing for the initiation of therapy, improves survival.

## METHODS

### STUDY DESIGN AND SETTING

We conducted a randomized, open-label, controlled trial of early initiation of antiretroviral therapy, as compared with the standard timing for initiation of therapy, among HIV-infected adults with a CD4+ T-cell count that was greater than 200 and less than 350 per cubic millimeter and no history of an AIDS illness. The primary study end point was survival. The study was conducted at the center of the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) in Port au Prince, Haiti.<sup>9</sup> The study was approved by the institutional review boards at Weill Cornell Medical College and GHESKIO. Two of the antiretroviral medications, zidovudine and lamivudine, were donated by GlaxoSmithKline, and one, lopinavir boosted by ritonavir, was donated by Abbott. (The other antiretroviral medications were do-

nated by the Global Fund to Fight AIDS, Tuberculosis, and Malaria.) Neither GlaxoSmithKline nor Abbott had a role in the design of the study, the accrual or analysis of the data, or the preparation of the manuscript.

### INCLUSION AND EXCLUSION CRITERIA

Subjects could be included in the study if they were infected with HIV, were at least 18 years of age, and had a confirmed CD4+ T-cell count that was greater than 200 and less than 350 per cubic millimeter within 45 days before enrollment. Subjects were excluded if they had a history of an AIDS-defining illness (stage 4 in the WHO staging system)<sup>10</sup> or had received antiretroviral therapy previously. Other inclusion and exclusion criteria are detailed in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

### RECRUITMENT AND RANDOMIZATION

Subjects were recruited at GHESKIO from August 2005 through July 2008. After the subjects had provided written informed consent,<sup>11</sup> the study team performed a screening evaluation, and eligible subjects were enrolled. Participants were randomly assigned with the use of a computer-generated random-numbers list, in a 1:1 ratio, to either early initiation of treatment (early-treatment group) or the standard timing for initiation of treatment (standard-treatment group).

### STUDY INTERVENTION

Subjects in both groups were seen monthly by a clinician and received the package of services provided to all HIV-1-infected patients at GHESKIO. Prophylactic treatment with trimethoprim-sulfamethoxazole was administered in all participants,<sup>12,13</sup> and isoniazid was given to those who had a positive purified protein derivative (PPD) skin test.<sup>14</sup> Participants received nutritional support that consisted of daily multivitamins and a monthly food basket containing rice, beans, oil, and meat.<sup>15</sup> To encourage participants to continue medical follow-up and remain in the study, field workers visited their residences at the time of enrollment and in the case of a missed visit. Participants were counseled about adherence to therapy and about the importance of returning to the clinic whenever they had symptoms.

If a participant had a cough or symptoms that were suggestive of tuberculosis at any time dur-

ing the study, a chest radiograph was obtained; in addition, three sputum smears were examined for acid-fast bacilli with the use of Ziehl-Neelsen staining and were cultured for *Mycobacterium tuberculosis* on Löwenstein-Jensen medium.<sup>16</sup> Subjects with active tuberculosis received directly observed therapy consisting of daily administration of four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) for a 2-month initiation phase, followed by daily administration of two drugs (isoniazid and rifampin) for a 4-month continuation phase.<sup>17,18</sup> Subjects with drug-resistant tuberculosis were treated according to WHO guidelines.<sup>19</sup>

The early-treatment group began treatment within 2 weeks after enrollment. Treatment consisted of lamivudine (150 mg every 12 hours) and zidovudine (300 mg every 12 hours), in a fixed-dose combination, and efavirenz (600 mg every 24 hours, at bedtime). For the first 2 months, antiretroviral therapy was provided under modified direct observation: receipt of the morning dose was observed at the study participant's home by a GHESKIO field worker; the evening dose was left with the participant and the participant was not observed while taking the medication.

If a drug caused toxic effects in a subject, the following drug substitution could be made: stavudine as a substitute for zidovudine and nevirapine or lopinavir, boosted by ritonavir, as a substitute for efavirenz. Among participants who were receiving rifampin for the treatment of active tuberculosis, the dose of efavirenz was increased from 600 mg every 24 hours to 800 mg every 24 hours. The failure of antiretroviral therapy was defined according to the WHO criteria: a confirmed decrease in the CD4+ T-cell count to a level that was 50% below the peak count or to a level below the baseline count, or a new AIDS illness during receipt of antiretroviral therapy.<sup>2</sup> Participants in whom first-line therapy failed were switched to the second-line regimen of abacavir, didanosine, and lopinavir boosted by ritonavir.

Participants in the standard-treatment group started therapy when they had a single CD4+ T-cell count of 200 per cubic millimeter or less or when an AIDS-defining illness developed. The treatment consisted of the same first-line regimen of antiretroviral therapy as that used for the early-treatment group (lamivudine, zidovudine, and efavirenz). In addition, for women in the standard-treatment group who became pregnant, antiretroviral therapy was initiated to prevent transmis-

sion of HIV to the fetus and was continued throughout the study, but nevirapine was substituted for efavirenz. Other drug substitutions and the second-line regimen were the same as those for the early-treatment group.

#### STUDY END POINTS

The primary study end point was survival. Death was documented in one of the following ways: an obituary notice, an autopsy report, a hospital death certificate, or a report from a contact documenting oral communication with the subject's health care provider or family member. Incident tuberculosis was a secondary study end point. We used the case definition of the American Thoracic Society, as described previously.<sup>16,20</sup>

#### CLINICAL AND LABORATORY MEASUREMENTS

Adherence to antiretroviral medications was measured with the use of a questionnaire about medication adherence, described previously, that was translated into Haitian Creole. The questionnaire was administered every 6 months.<sup>21</sup>

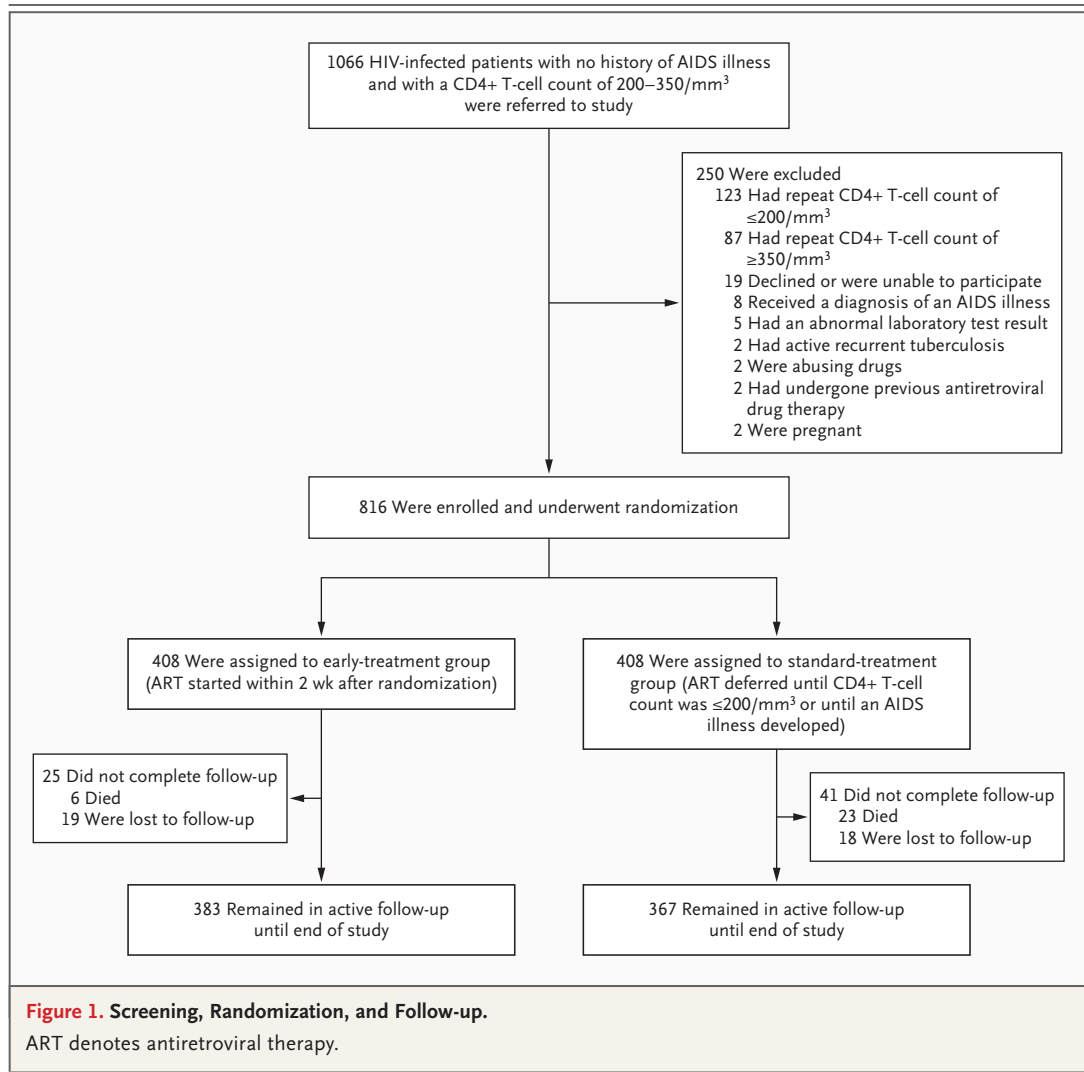
Serious adverse events and their relationship to antiretroviral medications were assessed, were graded according to the grading system in the National Institutes of Health, Division of AIDS, manual for the grading of adverse events, and were reported at the standard level of reporting.<sup>22</sup> We report all severe (grade 3) and life-threatening (grade 4) suspected drug reactions.

Laboratory tests that were performed included a baseline CD4+ T-cell count, a complete blood count, and measurements of aspartate aminotransferase, alanine aminotransferase, and creatinine. A complete blood count, liver-function tests, and serum chemical tests were repeated every 3 months for participants who were taking antiretroviral drugs. The CD4+ T-cell count was repeated for all participants every 6 months or more frequently, if requested by the primary care clinician.

#### STATISTICAL ANALYSIS

Information from clinical and laboratory case-report forms was entered electronically in Haiti through an Internet interface, and the data were managed by Frontier Science and Technology Research Foundation in New York. Data were exported into SAS software (SAS Institute) for analysis.

The study was designed to accumulate a fixed number of end points. We estimated that with a sample of 794 participants (397 per group), the



study would have 80% power to show a hazard ratio for survival with early treatment of 2.0 after 65 deaths had occurred, with a two-sided type I error rate of 5%. Three interim analyses were scheduled, after 16, 32, and 48 deaths had occurred. The interim analyses, which were performed by investigators who were unaware of the treatment assignments, were reviewed by members of the data and safety monitoring board of the National Institutes of Health, Division of AIDS. Prespecified stopping rules were based on the O'Brien–Fleming boundary for significance, with Lan–DeMets flexible spending functions.<sup>23</sup>

We hypothesized that early initiation of antiretroviral therapy, as compared with the standard timing for initiation of therapy, would improve survival. All analyses were based on the intention-to-treat principle. The primary study end point,

survival, was analyzed with the use of standard Kaplan–Meier methods, and differences between the two survival curves were evaluated with the use of the log-rank test, as specified in the protocol.<sup>24</sup> Cox proportional-hazards regression analysis was used to estimate the hazard ratio with 95% confidence intervals. We used the same methods in the analysis of the secondary outcome of incident tuberculosis. For comparison of other proportions, we used Fisher's exact test. Two-sided hypotheses and tests were adopted for all statistical inferences.

## RESULTS

### RECRUITMENT AND BASELINE CHARACTERISTICS

A total of 1066 subjects were screened between August 2005 and July 2008, and 816 were enrolled

in the study (Fig. 1). The median age of enrolled subjects was 40 years, and 470 (58%) were women. The median CD4+ T-cell count was 281 per cubic millimeter. The baseline characteristics were similar between the two groups (Table 1).

#### STATUS AT THE TIME OF ANALYSIS

The data and safety monitoring board reviewed the second interim analysis, which included data accumulated up to May 1, 2009; there were 29 deaths at that point. The trial crossed the pre-specified stopping boundary for a difference in survival between the groups, and the data and safety monitoring board recommended that the trial be stopped and that all participants in the standard-treatment group be given antiretroviral therapy.

The median length of follow-up was 21 months (range, 1 to 44). Of the 408 participants in the early-treatment group, 383 (94%) continued in follow-up to the end of the study, 6 (1%) died, and 19 (5%) were lost to follow-up. Of the 408 participants in the standard-treatment group, 367 (90%) were included in the follow-up assessments, 23 (6%) died, and 18 (4%) were lost to follow-up.

Of the 408 participants in the standard-treatment group, 160 (39%) met the criteria for initiation of antiretroviral therapy and began receiving antiretroviral drugs during the course of the study. Of the 408 participants in the standard-treatment group, 118 (29%) received isoniazid prophylaxis because of a positive tuberculin skin test and 400 (98%) received trimethoprim-sulfamethoxazole prophylaxis. Of the 408 participants in the early-treatment group, 99 (24%) received isoniazid prophylaxis and 388 (95%) received trimethoprim-sulfamethoxazole prophylaxis. Of the 327 participants in the early-treatment group who had at least 12 months of follow-up, 294 (90%) were adherent to antiretroviral therapy (i.e., received more than 95% of antiretroviral medications in the first year of antiretroviral therapy); of the 60 participants in the standard-treatment group who received antiretroviral therapy for at least 12 months, 57 (95%) were adherent to the therapy.

#### SURVIVAL

There were 29 deaths during the course of the study — 23 in the standard-treatment group and 6 in the early-treatment group ( $P=0.001$  by the log-rank test). In the Kaplan-Meier analysis, 98% of the participants in the early-treatment group and 93% in the standard-treatment group were

**Table 1. Baseline Characteristics of the Study Participants.**

Characteristic	Early Treatment (N=408)	Standard Treatment (N=408)
Age — yr		
Median	40	40
Interquartile range	34–46	32–47
Female sex — no. (%)	241 (59)	229 (56)
Education — no. (%)		
No school	133 (33)	120 (29)
Primary school	122 (30)	124 (30)
Secondary school or more	153 (38)	164 (40)
Annual income <\$100/yr — no. (%)	259 (63)	254 (62)
Living with spouse or partner — no. (%)	177 (43)	164 (40)
HIV clinical stage — no. (%)*		
Stage 1	135 (33)	126 (31)
Stage 2	199 (49)	219 (54)
Stage 3	74 (18)	63 (15)
Pulmonary tuberculosis — no. (%)	28 (7)	15 (4)
CD4 T-cell count — cells/mm <sup>3</sup>		
Median	280	282
Interquartile range	250–305	250–310
Body-mass index†		
Median	21.3	21.0
Interquartile range	19.6–23.7	9.2–23.4
Hemoglobin — g/dl		
Median	11.5	11.4
Interquartile range	10.3–12.6	10.3–12.5

\* The clinical stage of HIV was assessed according to the World Health Organization staging system,<sup>10</sup> which ranges from clinical stage 1 (no symptoms) to clinical stage 4 (AIDS).

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

alive at 36 months (Fig. 2). The unadjusted hazard ratio for the risk of death with standard treatment as compared with early treatment was 4.0 (95% confidence interval [CI], 1.6 to 9.8).

The causes of death among the 23 participants in the standard-treatment group who died were gastroenteritis (7 participants), tuberculosis (5), pneumonia (4), homicide (2), cancer (1), cardiomyopathy (1), cholangitis with sepsis (1), stroke (1), and suicide (1). The causes of death among the 6 participants in the early-treatment group who died were burn injury (1), gastroenteritis (1), myocardial infarction (1), pulmonary embolism after gynecologic surgery (1), stroke (1), and gastroin-

**CD4+ T-CELL COUNT**

The median CD4+ T-cell count in the early-treatment group increased from 280 per cubic millimeter at enrollment to 520 per cubic millimeter at month 36. The median CD4+ T-cell count in the standard-treatment group declined from 282 per cubic millimeter at baseline to 270 per cubic millimeter at month 36.

**INITIATION OF ANTIRETROVIRAL THERAPY IN THE STANDARD-TREATMENT GROUP**

Antiretroviral therapy was initiated in 160 of the 408 participants in the standard-treatment group (39%). In 147 of these participants, the CD4+ T-cell count fell to 200 per cubic millimeter or less; in 7 participants, an AIDS-defining illness developed; and in 3 participants, both an AIDS-defining illness developed and the CD4+ T-cell count fell to 200 per cubic millimeter or less. In addition, antiretroviral therapy was initiated in three pregnant women to prevent transmission of HIV infection to their offspring. Among the 160 participants in the standard-treatment group in whom antiretroviral therapy was initiated, the median CD4+ T-cell count at the start of antiretroviral therapy was 166 per cubic millimeter (interquartile range, 130 to 190).

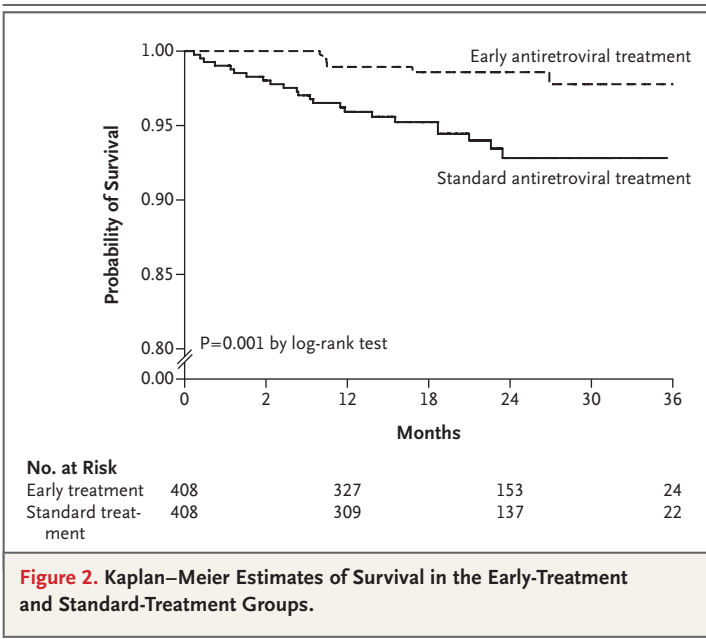
An additional 16 participants in the standard-treatment group died before antiretroviral therapy could be initiated. In the Kaplan–Meier analysis, the estimated median survival without antiretroviral therapy in the standard-treatment group was 24 months (Fig. 4).

**DRUG REACTIONS**

Of the 408 participants in the early-treatment group, 32 (8%) had a severe or life-threatening drug reaction. Of the 160 participants in the standard-treatment group who received antiretroviral therapy, 18 (11%) had a severe or life-threatening drug reaction. Details of these drug reactions are provided in Table 2 in the Supplementary Appendix. Anemia associated with zidovudine therapy was the most common adverse drug reaction, occurring in 13 (8%) of the 160 participants in the standard-treatment group who received antiretroviral therapy and in 14 (3%) of the 408 participants in the early-treatment group.

**DISCUSSION**

The results of this randomized, controlled trial show that among HIV-1-infected adults who live



**Figure 2.** Kaplan–Meier Estimates of Survival in the Early-Treatment and Standard-Treatment Groups.

testinal bleeding (1). There was only 1 death from an infectious disease in the early-treatment group, as compared with 17 deaths in the standard-treatment group.

Antiretroviral therapy had been initiated in 7 of the 23 participants in the standard-treatment group who died. These seven participants died a median of 2 months after starting therapy.

**INCIDENT TUBERCULOSIS**

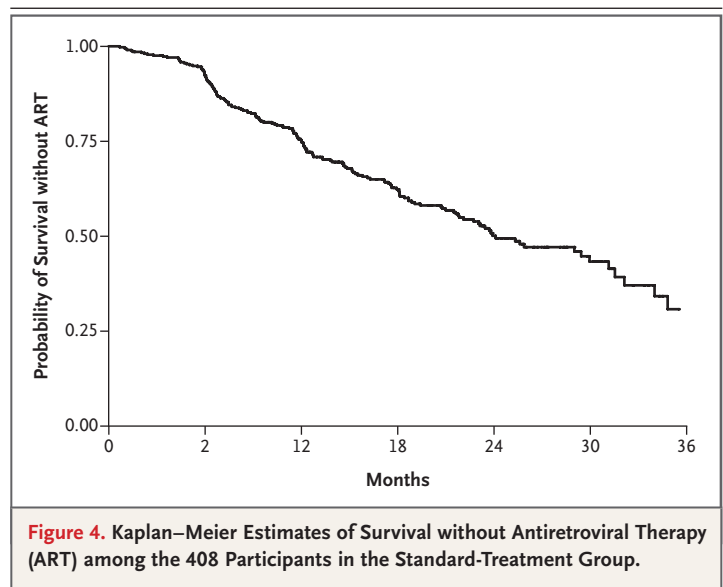
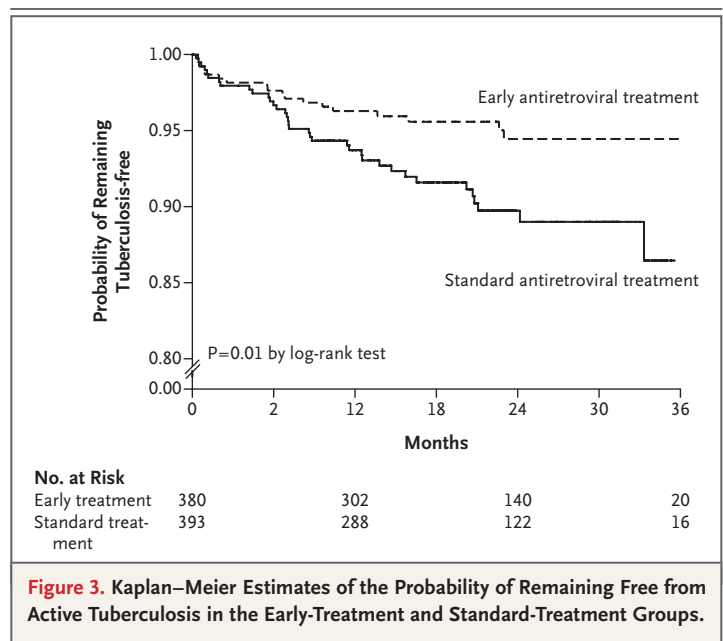
Among the 773 participants who did not have tuberculosis at enrollment, 54 received a diagnosis of tuberculosis during the follow-up period. There were 36 cases of incident tuberculosis in the standard-treatment group and 18 in the early-treatment group ( $P=0.01$  by the log-rank test). In the Kaplan–Meier analysis of survival, tuberculosis developed by 36 months in 6% of the participants in the early-treatment group, as compared with 14% in the standard-treatment group (Fig. 3). The hazard ratio for the risk of incident tuberculosis with standard treatment as compared with early treatment was 2.0 (95% CI, 1.2 to 3.6). Tuberculosis developed in 31 participants in the standard-treatment group before antiretroviral therapy was initiated and in 5 participants in the standard-treatment group a median of 6 months after the initiation of antiretroviral therapy. None of the participants in the early-treatment group, as compared with five of the participants in the standard-treatment group, died as a result of incident tuberculosis.

in resource-poor areas, antiretroviral therapy that is initiated when the CD4+ T-cell count is greater than 200 and less than 350 per cubic millimeter, as compared with antiretroviral therapy that is deferred until the CD4+ T-cell count falls to 200 per cubic millimeter or less or an AIDS-defining illness develops, results in a 75% reduction in the rate of death and a 50% decrease in the incidence of tuberculosis

Our finding that early antiretroviral therapy improves the rate of survival is consistent with data from observational studies.<sup>25,26</sup> The When To Start Consortium examined outcomes for more than 24,000 HIV-infected patients in 15 cohorts in Europe and North America. This study showed that with initiation of antiretroviral therapy when the CD4+ T-cell count was lower than 350 per cubic millimeter, as compared with initiation when the CD4+ T-cell count was 350 or higher, the hazard ratio for death was 1.4 to 2.0.<sup>26</sup> Our prospective study validates these observational findings in a randomized, controlled trial. Furthermore, the effect size in our trial, with a hazard ratio of 4.0, was larger than the effect size seen in the observational cohorts. One possible reason for the large effect size in our study is that it was conducted in a resource-poor setting, where high rates of tuberculosis, malnutrition, and coinfections with tropical diseases may exacerbate the effect of deferred therapy.

Early antiretroviral therapy also decreased the incidence of tuberculosis by 50% in our study. This finding is consistent with observational studies from Africa showing a decrease in the incidence of tuberculosis after antiretroviral therapy is started.<sup>27-29</sup> Tuberculosis is a leading cause of death among HIV-1-infected patients in developing countries,<sup>30</sup> and the effect of early antiretroviral therapy on the incidence of tuberculosis explains in part the decreased rate of death seen in our trial. Furthermore, the HIV epidemic has dramatically increased the incidence of active tuberculosis in countries with limited resources and is overwhelming tuberculosis-control programs.<sup>31</sup> Provision of early antiretroviral therapy on a large scale in areas with limited resources has the potential to decrease the incidence of active tuberculosis in the general population.

The WHO has promoted a public health approach in its guidelines to antiretroviral therapy, emphasizing feasibility, cost-effectiveness, and large-scale implementation.<sup>32</sup> Earlier initiation of antiretroviral therapy — when the CD4+ T-cell



count is less than 350 per cubic millimeter — is likely to be consistent with this approach.<sup>33</sup> The median time to the initiation of antiretroviral therapy in our standard-treatment group was 2 years. At current pricing, 2 years of antiretroviral drugs will cost approximately \$400 per person. Thus, for a cost of approximately \$400 per person, the rate of death can be decreased by 75%, and the incidence of active tuberculosis by 50%. Furthermore, the standard-treatment group had higher rates of infectious diseases and of treat-

ment-limiting drug reactions than did the early-treatment group and required frequent monitoring of CD4+ T-cell counts. This complex medical care consumed resources and the time of highly trained health care workers, factors that may in part offset the cost of starting antiretroviral therapy earlier.

Our study was not blinded. This would not affect the primary study end point of survival, but we cannot exclude the possibility that detection bias influenced the secondary end points. However, the rates at which participants remained in the study for follow-up assessments were high, and the fact that the rates were similar in the two groups suggests that the intensity of follow-up was similar.

In conclusion, early antiretroviral therapy decreased the rate of death by 75% in HIV-infected

adults who had a CD4+ T-cell count that was greater than 200 and less than 350 per cubic millimeter. Access to antiretroviral therapy should be expanded to all HIV-infected adults who have a CD4+ T-cell count of less than 350 per cubic millimeter, including those who live in locations with limited resources.

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