MAJOR ARTICLE

A Randomized Trial of Punctuated Antiretroviral Therapy in Ugandan HIV-Seropositive Adults With Pulmonary Tuberculosis and $CD4^+$ T-Cell Counts of ≥350 cells/μL

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(See the editorial commentary by Von Reyn, on pages 817–9.)

Background. Optimal treatment of human immunodeficiency virus (HIV)–associated tuberculosis in patients with high $CD4^+$ T-cell counts is unknown. Suppression of viral replication during therapy for tuberculosis may block effects of immune activation on T cells and slow HIV disease progression.

Methods. We conducted a randomized trial in 214 HIV-infected patients with active tuberculosis and $CD4^+$ T-cell counts of ≥350 cells/μL to determine whether 6 months of antiretroviral therapy given during tuberculosis treatment would improve clinical outcomes. Subjects were randomized to receive 6 months of abacavir-lamivudine-zidovudine concurrent with tuberculosis therapy or delayed antiretroviral therapy. Endpoints were $CD4^+$ T-cell counts of <250 cells/μL, AIDS, or death.

Results. Intervention and comparison arms had similar median $CD4^+$ counts (517 and 534 cells/μL, respectively) and HIV RNA levels (4.6 and 4.7 $\log_{10}$ copies/μL, respectively). Viral suppression was achieved in 86% of patients allocated to intervention. Seventeen subjects (15.6%) in the intervention arm developed study outcome compared to 25 subjects (22.8%) in the comparison arm ($P = .17$). Grade 3 or 4 adverse events were less frequent in the intervention arm. By 2 months, 90% of subjects in both arms were culture-negative for tuberculosis.

Conclusions. Short-term antiretroviral therapy during tuberculosis treatment in patients with $CD4^+$ T-cell counts of >350 cells/μL was safe and associated with clinical benefits.

The epidemics of tuberculosis and human immunodeficiency virus type 1 (HIV) infection converged with the greatest intensity in sub-Saharan Africa. Both the incidence and the prevalence of tuberculosis increased as the HIV infection epidemic swept through the continent. In Africa today, tuberculosis may affect up to 30% of coinfected persons [1] and is the leading cause of death. Even with effective antituberculosis treatment, case fatality rates for tuberculosis may be as high as 20%, especially in the face of severe immunosuppression [2, 3]. Moreover, tuberculosis may accelerate the clinical course of HIV infection and lead to poor outcomes [4–7].

Newly revised guidelines from the World Health Organization (WHO) recommend the use of antiretroviral therapy for all HIV-seropositive persons with tuberculosis disease, regardless of their $CD4^+$ T-cell count [8]. Recent evidence indicates that antiretroviral therapy should be started early in the course of tuberculosis treatment because it improves survival [9, 10]. Although there is abundant information on the benefit of antiretroviral therapy in HIV-infected tuberculosis patients with advanced immunosuppression [11–13], there are fewer data on the optimal management of

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tuberculosis among patients with $CD4^+$ T-cell counts of >350 cells/μL.

The present study was designed in the early years of the antiretroviral therapy rollout in Africa to determine whether a 6-month course of antiretroviral therapy given concurrently with tuberculosis treatment would improve the clinical, immunologic, and virologic outcomes among patients with $CD4^+$ T-cell counts of >350 cells/μL. The rationale of the study was that a punctuated course of antiretroviral therapy in patients with high $CD4^+$ T-cell counts would suppress viral replication during therapy for tuberculosis, block the effects of immune activation on T cells harboring HIV, slow the pace of HIV disease progression, and improve clinical outcomes. Although treatment interruption is no longer a viable option given recent advances in the field of HIV infection management [14], the present study provides evidence of clinical benefit when starting antiretroviral therapy in tuberculosis patients with preserved immunity.

METHODS

Study Design and Population

This study was an open-labeled, randomized clinical trial designed to determine whether a 6-month course of antiretroviral therapy given concurrently with tuberculosis treatment would improve clinical, immunologic, and virologic outcomes among HIV-infected patients with active tuberculosis and $CD4^+$ T-cell counts of >350 cells/μL. HIV-infected patients aged 13–60 years with their initial episode of sputum-smear-positive or culture-positive pulmonary tuberculosis were recruited through the local medical clinics in Kampala, Uganda, and the Tuberculosis Clinic at Mulago Hospital in Kampala, Uganda. Patients were eligible for the study if they had $CD4^+$ T-cell counts of >350 cells/μL, lived in the greater Kampala metropolitan area, and gave informed consent. Patients were excluded if they had a prior history of tuberculosis, multidrug-resistant tuberculosis, a WHO stage IV AIDS-defining condition, pregnancy, and/or prior use of antiretroviral therapy except for single-dose nevirapine. Other exclusions included hemoglobin level of <9.5 g/dL, absolute neutrophils count of <1000 cells, serum aspartate aminotransferase level of >2 times the upper limit of normal, serum creatinine level of >2.5 times the upper limit of normal, Karnofsky performance status of <60%, and weight of <40 kg.

Intervention and Randomization

Study subjects were randomized to receive either abacavir (300 mg), lamivudine (150 mg), and zidovudine (300 mg; Trizivir; GlaxoSmithKline) twice daily for 6 months (1 dose was observed by the study staff, and 1 dose was self-administered each day) or delayed antiretroviral therapy that was started when the subject reached a primary study endpoint. Random assignment of short-course antiretroviral therapy was performed between 2 and 4 weeks after starting tuberculosis treatment and after assessing safety and readiness to start antiretroviral therapy. Study intervention was allocated randomly through the statistical center at the University of California, San Francisco, in a 1:1 ratio using a permuted-block size of 16 to minimize the likelihood of unbalanced groups.

All eligible patients started standard treatment for tuberculosis (doses adjusted for weight), which included isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by isoniazid and rifampin for 4 months. Medication was given as directly observed therapy. Treatment was extended for 3 months for patients with persistent positive sputum cultures after 2 months of intensive therapy.

Outcome Assessment

The primary outcome for the study was the progression of HIV disease. Disease progression was measured using a composite endpoint including 1 or more of the following individual endpoints, whichever occurred first: $CD4^+$ T-cell count of <250 cells/μL on 2 occasions within a 3-month period; development of an AIDS-defining condition as determined using a modified WHO staging system; or death. The clinical histories of subjects reaching a primary endpoint were reviewed by an independent panel of 3 experts blinded to treatment assignment. This panel made the final determination of endpoint and the date of the primary endpoint. Secondary outcomes included response to tuberculosis treatment as measured by culture conversion by 2 months, treatment completion, tuberculosis relapse, and safety, especially the occurrence of abacavir hypersensitivity syndrome and immune reconstitution syndrome.

Follow-up and Measurements

Study subjects were evaluated monthly during the first year and quarterly thereafter. The planned duration of follow-up was 3 years, although individual observation time varied depending on the date of study enrollment. Home health visitors contacted subjects who missed scheduled appointments and encouraged them to return to the clinic. Demographic and clinical information was obtained through standardized interviews, and physical examinations were performed by trained medical officers. Sputum samples were collected for microscopy (Ziehl-Neelsen method) and mycobacterial culture (liquid culture with BACTEC and 7H10 solid medium) at screening; at 1, 2, 5, 12, and 18 months; and as clinically indicated. Drug susceptibility testing was performed on the initial isolate.

HIV testing was performed using sequential testing of 3 rapid tests [15] and confirmed with Western blot analysis. HIV RNA levels were measured using the Roche Amplicor assay, which had a minimal level of detection of 400 copies/μL. Blood samples were collected for complete blood count with differential counts (Coulter 450 system) and $CD4^+$ T-cell counts (EPICS Profile 2

flow cytometry). Analytic chemistry and urine pregnancy testing were performed. Posterior-anterior chest radiography was performed at baseline and at 6 months and was graded by reviewers blinded to treatment assignment.

Statistical Analysis

All analyses were performed using the intent-to-treat principle; sensitivity analyses were performed using a per-protocol analysis. In the main analysis, failure-time distributions from enrollment until the primary outcome were estimated using Kaplan-Meier methods and compared between groups by use of the Wilcoxon test at 6, 12, and 24 months. Study subjects were censored at the time of study withdrawal or end of trial. Cox proportional hazards models were used to estimate the efficacy of the intervention. Mean values for HIV RNA levels and $CD4^+$ T-cell counts were compared using the sign rank test or mixed effects linear regression models. The safety of the intervention was determined by comparing the cumulative proportion of grade 3 or 4 adverse events between arms using the χ^2 or Fisher exact test. The response to antituberculosis therapy was evaluated by comparing the proportion of subjects with positive sputum smear or culture at 1, 2, and 5 months and by comparing the incidence of recurrent disease.

The trial was initially designed to detect a 30% difference in the primary outcome with a power of 90% and error of 5% with a sample size of 150 patients per arm. Because of slow, but gradual, recruitment and the limited period of the trial, the sample size was reduced to 110 patients per arm with 80% power to detect a 50% difference in the primary outcome.

This project was approved by the institutional review boards at the University of Georgia; Case Western Reserve University; University of California, San Francisco; the Joint Clinical Research Center; and the Uganda Council for Science and Technology. The sponsors of the study did not participate in the study design, data collection, analysis, interpretation, or writing of this report.

RESULTS

Study Population

From October 2004 through September 2008, 4951 patients were screened for the trial and 250 were enrolled (Figure 1). Most

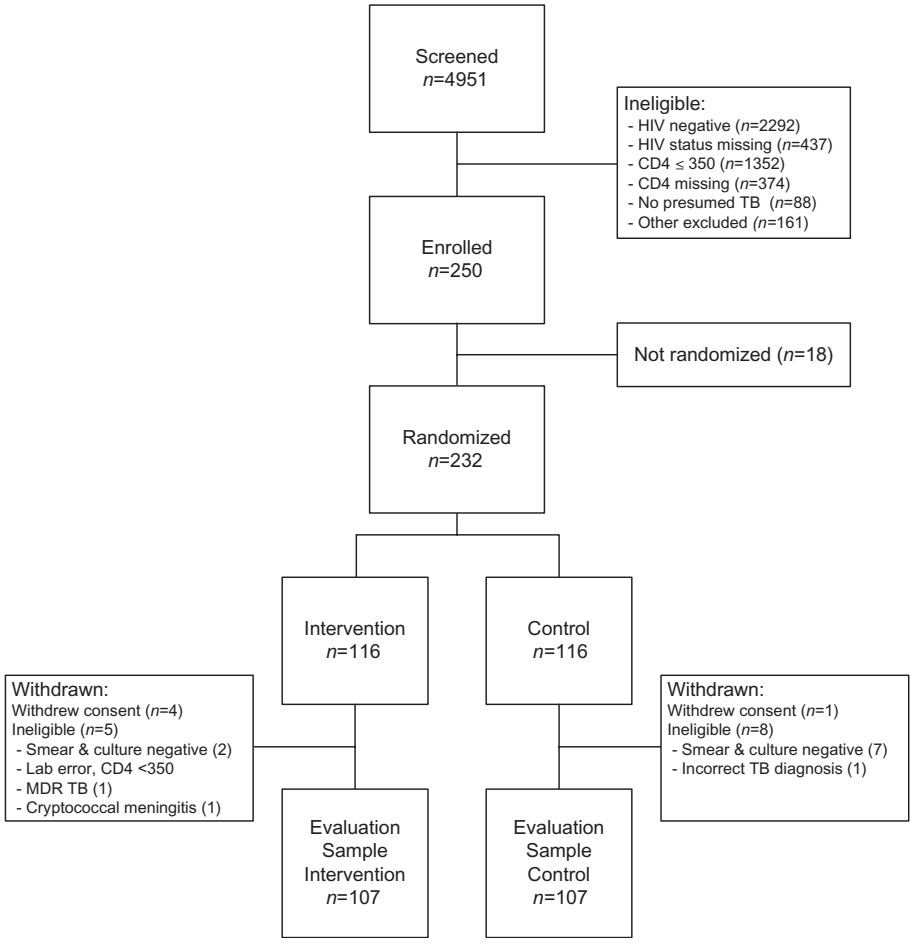

Figure 1. Summary of study recruitment, enrollment, exclusions, and follow-up for a randomized clinical trial of punctuated antiretroviral therapy in human immunodeficiency virus (HIV)–infected patients with tuberculosis (TB) in Kampala, Uganda, 2004–2009. MDR TB, multidrug-resistant tuberculosis.

Table 1. Baseline Demographic and Clinical Characteristics by Treatment Arm According to Study Arm for 214 Patients With HIV-Associated Tuberculosis Presenting at Mulago Hospital Tuberculosis Clinic From 2004 to 2008

Characteristic	Intervention arm (n = 107)	Control arm (n = 107)
Men	56 (52)	67 (63)
Karnofsky performance status		
100	0 (0)	1 (1)
90	43 (40)	43 (40)
80	59 (55)	58 (54)
70	5 (5)	5 (5)
Symptoms		
Cough	105 (98)	107 (100)
Chest pain	74 (69)	78 (73)
Purulent sputum	82 (77)	77 (72)
Hemoptysis	11 (10)	11 (10)
Fever	78 (73)	78 (73)
Sweats	68 (64)	79 (74)
Weight loss	80 (75)	86 (80)
Physical examination findings		
Consolidation	76 (71)	77 (72)
Wheezing or rhonchi	8 (7)	4 (4)
Pleural effusion	2 (2)	2 (2)
Lymphadenopathy	27 (25)	32 (30)
Radiographic findings		
Cavitary disease	73 (68)	62 (58)
Fibrosis	9 (8)	13 (12)
Pleural effusion	3 (3)	10 (9)
Miliary disease	3 (3)	3 (3)
Hilar adenopathy	0 (0)	5 (5)
Extent of disease		
Normal	2 (2)	5 (5)
Minimal	17 (16)	17 (16)
Moderate	26 (24)	33 (31)
Advanced	62 (58)	52 (49)
Microbiological results[a]		
Smear positive and culture positive	96 (90)	93 (87)
Smear positive and culture negative	8 (8)	8 (8)
Smear negative and culture positive	2 (2)	5 (5)
Culture positive	98 (92)	98 (92)
Age in years, mean (SE)	31 (0.70)	32 (0.83)
BMI, kg/m^2, mean (SE)	19.8 (0.25)	19.8 (0.24)
Hemoglobin level, g/dL, mean (SE)	12.1 (0.14)	12.1 (0.18)
AST level, IU/L, mean (SE)	25 (1.16)	25 (1.07)
$CD4^+$ T-cell count, cells/μL		
Mean (SE)	561 (19.8)	583 (22.5)
Median (IQR)	517 (414–640)	534 (407–662)
HIV RNA level, $\log_{10}$ copies/μL		
Mean (SE)	4.5 (0.09)	4.5 (0.09)
Median (IQR)	4.6 (4.1–5.1)	4.7 (4.0–5.2)
WBC count	7.8 (0.23)	7.8 (0.24)
Lymphocyte count	2.2 (0.07)	2.6 (0.09)

NOTE. Data are no. (%) of patients, unless otherwise indicated. AST, aspartate aminotransferase; BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; SE, standard error; WBC, white blood cell.

[a] Two baseline microbiologic samples are missing, 1 from each arm. The denominator for smear- and culture-positive proportions is 106 in each arm.

patients were excluded because they were HIV seronegative (n = 2292) or had $CD4^+$ T-cell counts of <350 cells/μL (n = 1352). The remaining 1307 patients were excluded because of missing HIV test results, missing $CD4^+$ T-cell counts, no active tuberculosis, and other miscellaneous reasons. Of the 250 patients enrolled, 232 were randomized, yielding 116 subjects in each study group; 18 subjects were not randomized because of safety concerns about starting antiretroviral therapy; and 18 withdrew or were found ineligible. Of the 107 patients in the intervention arm, 71 (66%) were randomized and began antiretroviral therapy by 2 weeks, 27 (25%) by 3 weeks, and 9 (8%) by 4 weeks; of the 107 patients in the comparison arm, 63 (59%) were randomized by 2 weeks, 32 (30%) by 3 weeks, and 12 (11%) by 4 weeks. At the close of the study, there were 214 evaluable subjects, with 107 subjects in each arm, after 9 exclusions from the intervention arm and 9 exclusions from the control arm.

The demographic and clinical characteristics were similar at the baseline in terms of age, body mass index, Karnofsky performance status, $CD4^+$ T-cell count, HIV RNA level, symptoms at presentation, chest radiography, smear microscopy, and mycobacterial culture (Table 1). The intervention and control arms were balanced in terms of median $CD4^+$ T-cell count (517 and 534 cells/μL, respectively) and median viral load (4.6 and 4.7 $\log_{10}$ copies/mL, respectively).

Event-Free Survival

During a mean of 23.3 months of observation, 42 subjects developed the primary composite endpoint, 17 in the immediate short-course arm and 25 in the delayed arm. The majority of subjects who reached the primary endpoint did so on the basis of $CD4^+$ T-cell count criteria; 15 subjects in the immediate arm and 18 in the delayed arm were identified and began lifelong antiretroviral therapy. At the end of the trial, there were no clinical endpoints and 2 deaths in the immediate treatment arm and 3 clinical endpoints and 4 deaths in the delayed arm.

Overall, for the composite endpoint, the event-free survival distributions did not differ between the 2 study arms (P = .17; Wilcoxon test) (Figure 2); however, the event-free survival was

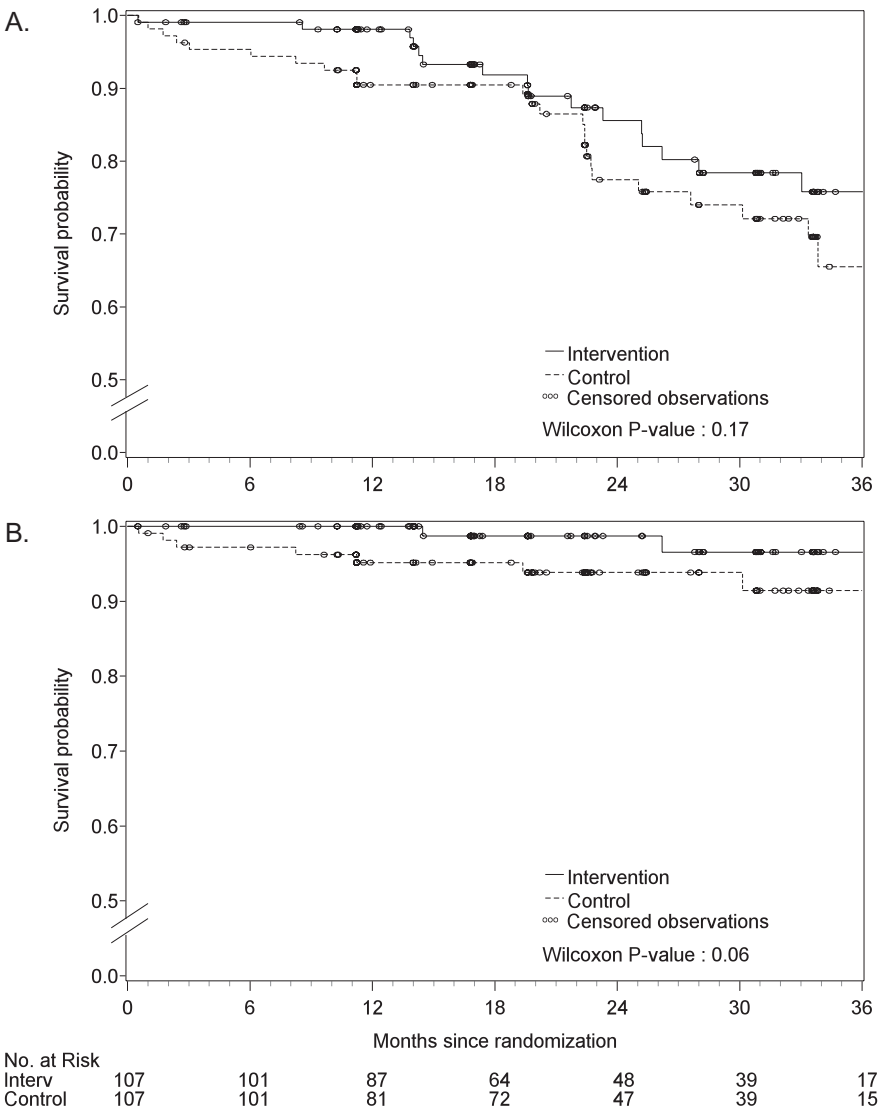

Figure 2. *A,* Kaplan-Meier estimates of event-event free survival using a composite endpoint ($CD4^+$ T-cell count of 250 cells/μL, clinical AIDS, or death), comparing the intervention and control arms (Wilcoxon test). *B,* Kaplan-Meier estimates of event-event free survival using clinical AIDS or death as endpoints, comparing the intervention and control arms (Wilcoxon test).

consistently higher in the immediate arm than in the delayed arm throughout the course of follow-up. The observed effect of the intervention varied over time. At 6 months, when the intervention was completed, there was a marginal difference in event-free survival in the intervention and control arms (99% and 95%, respectively; $P = .108$; Wilcoxon test) that became statistically significant at 12 months (98% and 90%, respectively; $P = .02$; Wilcoxon test). By 24 months, the event-free survival patterns in the 2 arms were similar. There was an overall reduction in the primary endpoint of 32% (95% confidence interval (CI), 26%–63%) in the intervention arm compared with that in the control arm.

For the clinical endpoints (AIDS or death) not including $CD4^+$ T-cell counts, there were similar patterns in outcome, but a difference in event-free survival between arms was present at 12 months (95% and 100%; $P = .026$) and persisted over the 2 years of observation ($P = .048$; Wilcoxon test) (Figure 2). There was a 71% reduction in the clinical outcomes (95% CI, 38%–94%) in the intervention arm compared with that in the control arm.

Effect of Antiretroviral Intervention: Longitudinal Analysis

Subjects randomized to the immediate therapy arm achieved rapid suppression of HIV RNA levels (Figure 3). At both 3 and 6 months, the HIV RNA levels of 86% of patients were suppressed to <400 copies/μL. As expected, the HIV RNA levels rebounded upon discontinuation of antiretroviral therapy to near baseline levels, where they remained stable for the duration of the study. HIV RNA levels in the control group remained unchanged on average during 24 months of follow-up.

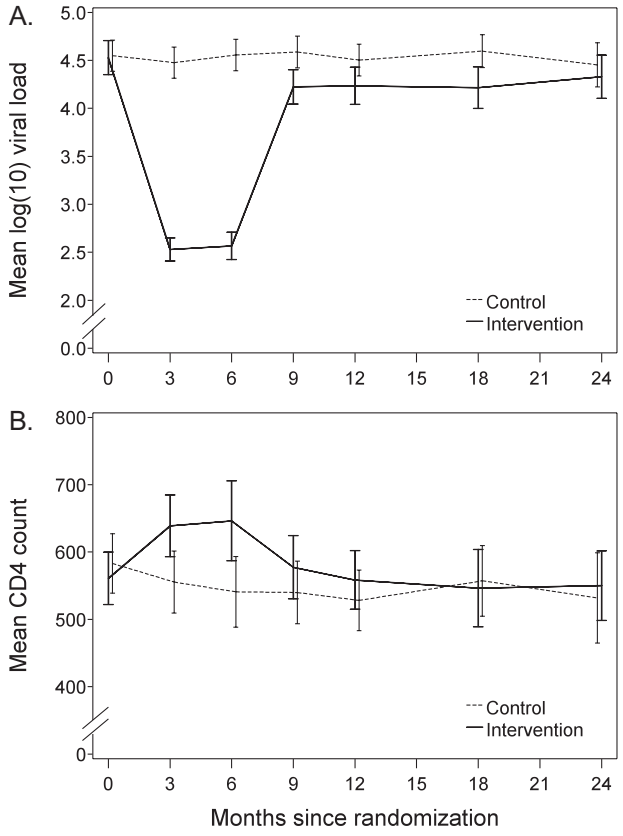

Figure 3. *A,* Mean levels of human immunodeficiency virus (HIV) RNA (copies per microliter; standard errors) for intervention and control arms during 3 years of observation. *B,* Mean $CD4^+$ T-cell counts (cells per microliter; standard errors) for intervention and control arms during 3 years of observation.

The intervention also resulted in a gradual increase in $CD4^+$ T-cell counts (Figure 3) between baseline and 6 months. In patients receiving antiretroviral therapy, the slope in $CD4^+$ T-cell counts increased by 2.5 cells/μL per month, whereas in patients in the delayed treatment arm, $CD4^+$ T-cell counts declined by 2.5 cells/μL per month ($P = .04$). After discontinuing antiretroviral therapy in the intervention arm, the $CD4^+$ counts returned to baseline levels within 3 months, were similar to those in the untreated group, and remained stable for the duration of follow-up.

Adverse Effects

During the course of the study, nearly all subjects experienced at least 1 graded adverse event during the course of the trial. Grade 2, or moderate, adverse events were the most common, occurring in about one-half of the subjects in each arm. The cumulative proportion of individuals who experienced a grade 3 or 4 adverse event was lower in the intervention arm than in the control arm (26% and 42%, respectively; $P = .01$) (Table 2). Hematologic adverse events predominated the adverse event profile. There were 5 subjects who experienced severe or life-threatening anemia and 6 subjects with thrombocytopenia. The most common severe adverse event was neutropenia, which occurred in 18 subjects in the intervention arm and 25 in the control arm. When adverse events were considered individually, the overall risk of a grade 3 or 4 adverse event was 76% greater in the control arm than in the intervention arm (rate ratio, 1.76; 95% CI, 1.24–2.53). The proportion of grade 3 or 4 adverse events occurring during the intervention period of the study was 48%. During the study, 18 women became pregnant despite counseling to use 2 methods of contraception. Ten pregnancies occurred in the intervention arm and 8 in the delayed treatment arm; 4 pregnancies occurred during tuberculosis treatment, 2 pregnancies in each arm. No cases of immune reconstitution inflammatory syndrome were detected.

Table 2. Highest Grade Adverse Event Experienced by 214 Patients With HIV-Associated Tuberculosis According to Study Arm

Adverse event	Intervention arm ($n = 107$)	Control arm ($n = 107$)
Any adverse event		
Normal	3 (3)	1 (1)
Mild	22 (21)	7 (7)
Moderate	54 (50)	54 (50)
Severe	18 (17)	32 (30)
Life-threatening	10 (9)	13 (12)
Grade 3 or 4 adverse event		
Anemia	3 (3)	2 (2)
Neutropenia	18 (17)	25 (23)
Thrombocytopenia	2 (2)	4 (4)
Cardiac arrhythmia	0 (0)	2 (2)
Hypotension	2 (2)	1 (1)
Hypertension	0 (0)	1 (1)
Congestive heart failure	0 (0)	1 (1)
Diarrhea	0 (0)	1 (1)
Peptic ulcers	0 (0)	1 (1)
Ascites	1 (1)	0 (0)
Lobar pneumonia	0 (0)	1 (1)
Neuro-motor abnormality	0 (0)	3 (3)
Psychiatric disorder	1 (1)	1 (1)
Elevated AST level	3 (3)	4 (4)
Rash	3 (3)	5 (5)

NOTE. Data are no. (%) of patients. AST, aspartate aminotransferase; HIV, human immunodeficiency virus.

Response to Antituberculosis Therapy

In both the intervention and control arms, 92% of subjects had a positive culture for *Mycobacterium tuberculosis* and the remaining 8% tested positive by sputum smear (Table 1). After 2 months of antituberculosis therapy, ~10% of subjects remained culture positive (no difference between arms), and after 6 months of standard therapy, none had positive cultures. The median time to culture conversion was 37.5 days in

the intervention arm and 29 days in the control arm ($P = .37$; log-rank test). Throughout treatment, the proportion of subjects with a positive sputum smear was consistently higher than the proportioin of subjects with positive culture. After 2 months of therapy, ~45% of subjects remained smear positive (no difference between arms), and after 5 months of standard therapy, 19% remained smear positive. The median time to sputum smear conversion was 43 days in the intervention arm and 42 days in the control arm ($P = .27$; log-rank test). During follow-up, 7 cases of recurrent tuberculosis occurred, 3 in the intervention arm and 4 in the control arm ($P = .5$).

DISCUSSION

In this randomized, open-labeled, clinical trial of antiretroviral therapy during treatment of active tuberculosis among HIV-infected patients with $CD4^+$ T-cell counts of >350 cells/μL, we found that a punctuated course of antiretroviral therapy provided measureable, but only short-term, clinical benefits. The intervention reduced the incidence of the composite clinical and immunologic outcome at 12 months and reduced the incidence of AIDS and death over 24 months. The clinical improvement corresponded with viral suppression and increased $CD4^+$ T-cell counts. The intervention did not interfere with successful treatment of tuberculosis and was well-tolerated because few serious adverse events attributable to the intervention were observed.

Most HIV-infected persons with active tuberculosis present with low $CD4^+$ T-cell counts and warrant antiretroviral therapy on the basis of $CD4^+$ T-cell count criteria alone. Initiation of antiretroviral therapy with the treatment of tuberculosis affords benefit to patients with $CD4^+$ T-cell counts of <250 cells [9, 10]. About one-quarter of HIV-infected patients with tuberculosis, however, present with higher $CD4^+$ T-cell counts of >350 cells/μL, and the evidence for benefit of antiretroviral therapy in this group is less well studied. Although antiretroviral therapy appears to be beneficial in patients with higher $CD4^+$ T-cell counts, observational studies suffer from confounding by indication [16, 17], and the 1 randomized clinical trial of tuberculosis management is limited by small group sizes and few outcomes in the higher $CD4^+$ T-cell count strata [9]. The findings from our study provide limited but further support for the early initiation of antiretroviral therapy, even among those with preserved immunity. During the period of intervention, viral replication was suppressed and $CD4^+$ T-cell counts increased compared with those of patients who were not initially treated with antiretroviral therapy. Moreover, there was a tendency toward fewer clinical events. The present study does not provide evidence of long-term benefit because of the short duration of the intervention; however, based on the clinical effectiveness of antiretroviral therapy seen in large cohort studies of HIV-associated tuberculosis [18], one would expect benefits to continue to accrue with lifelong antiretroviral therapy treatment.

The premise of this study was based on the copathogenesis model of HIV and *Mycobacterium tuberculosis*. This model posits that cellular immune activation induced by tuberculosis leads to enhanced viral replication, loss of $CD4^+$ T cells, and progression of HIV infection [19]. Previous trials aimed at modulating immune activation failed to produce lasting effects on surrogate endpoints or clinical outcomes [20–22]. The present study was designed to interrupt the final step in the bidirectional interaction by suppressing viral replication induced by immune activation due to tuberculosis. For the composite outcome, including immune suppression, we observed a 32% reduction in disease progression with the intervention group compared with the comparison group, but this difference did not reach statistical significance because the enrolled sample was smaller than planned; hence, the study was underpowered to detect this level of effect. Of note, most of this effect occurred during the first year and was attributable to the $CD4^+$ T-cell counts falling to <250 cells/μL; by the end of follow-up, the groups had similar numbers of $CD4^+$ T-cell endpoint events. When the clinical outcomes of AIDS and death were evaluated, the effect was even greater (71%), but again, the study was underpowered to show this effect. Although the findings were not statistically significant, the magnitude and direction of the effect were consistent with this model.

In the planning of the study, we opted to use the triple-nucleoside combination of abacavir, lamivudine, and zidovudine because it was considered a potential future therapeutic option in Uganda. During the early phases of the trial, a seminal study showed that the inclusion of a nonnucleoside reverse-transcriptase inhibitor was more potent in suppressing viral replication than a combination using 3 nucleoside reverse-transcriptase inhibitors [23]. This seminal study was not conducted in patients with tuberculosis or exclusively high $CD4^+$ T-cell counts. This is important because these patients can experience medication toxicity with nevirapine and drug interactions with protease inhibitors. We continued to use the triple-nucleoside combination in the study because it was safe during pregnancy, had a reduced pill burden, and theoretically had a lower risk of drug resistance after treatment interruption compared with efavirenz-based regimens. Early close monitoring indicated excellent suppression of HIV RNA levels by 6 months in 86% of people receiving therapy [24]. Although we observed excellent suppression of HIV RNA replication to the level of 400 copies/μL, it is possible that the intervention did not entirely suppress replication. Incomplete suppression of replication would mitigate the effect of the intervention and bias the results toward observing no difference between arms.

In this study, the intervention group experienced fewer severe or life-threatening adverse events. The most common severe adverse event was neutropenia, which occurred with greater

frequency in the delayed treatment arm. Neutropenia in HIV-infected persons may result from the effects of HIV on hematopoiesis [25] or from the effects of other HIV-related conditions and medications [26]. The findings of this study indicate that neutropenia is common in patients with tuberculosis, even when $CD4^+$ T-cells counts are >350 cells/μL. Moreover, it indicates that treatment with concurrent antiretroviral therapy only partially mitigates the effect of HIV infection on bone marrow suppression [27].

Since the study began in 2004, 2 important developments in the field of HIV infection therapeutics have affected the interpretation of our results. First, the Strategies for Management of Antiretroviral Therapy study showed that episodic or interrupted antiretroviral therapy was associated with poor clinical outcomes [14]. Although our study was not designed as a structured treatment interruption trial, the idea of discontinuing antiretroviral therapy once it has started is no longer tenable. Second, recent evidence from randomized clinical trials in resource-limited settings [28] and large cohort studies in industrialized countries [29, 30] indicate that earlier initiation of therapy delays AIDS and prolongs survival. These studies found that a $CD4^+$ T-cell count of 350 cells/μL was a minimum threshold for starting antiretroviral therapy. In light of these findings, it is unlikely that the intervention as tested in this study will be acceptable in current practice.

In conclusion, our study provides new and relevant information on the management of tuberculosis in HIV-infected patients with high $CD4^+$ T-cell counts. Antiretroviral therapy can be administered safely to these patients at the onset of antituberculosis therapy without interfering with treatment for tuberculosis. Triple nucleosides appear to be safe and effective, supporting their use when other options are not available or contraindicated. Further studies are needed to determine whether the clinical, virologic, and immunologic benefits observed in this study are maintained with continual, daily antiretroviral therapy in patients successfully treated for tuberculosis with $CD4^+$ T-cell counts of >350 cells/μL.

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