Mycobacterium tuberculosis Microbiologic and Clinical Treatment Outcomes in a Randomized Trial of Immediate versus CD4$^+$-Initiated Antiretroviral Therapy in HIV-Infected Adults with a High CD4$^+$ Cell Count

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In a prospective randomized, controlled trial in Uganda comparing the efficacy of antiretroviral therapy during tuberculosis therapy with the efficacy of tuberculosis therapy alone in HIV-infected patients with tuberculosis who have a CD4$^+$ cell count >350 cells/μL, it was found that antiretroviral therapy did not accelerate microbiologic, radiographic, or clinical responses to tuberculosis therapy: 18% of participants had sputum smears positive for *Mycobacterium tuberculosis* after 5 months of tuberculosis therapy, despite having had negative culture results.

Trial registration. **ClinicalTrials.gov identifier: NCT00078247.**

Recent World Health Organization (WHO) guidelines recommend antiretroviral therapy (ART) for all persons with active tuberculosis (TB) regardless of CD4$^+$ cell count, to delay progression of human immunodeficiency virus (HIV) infection [1]. In a prospective, randomized controlled trial in Uganda, we sought to determine whether ART during TB therapy accelerates clinical, radiographic, and microbiologic outcomes, compared with TB therapy alone, in HIV-infected patients with pulmonary TB who have a CD4$^+$ cell count >350 cells/μL. We also examined patients with sputum smears positive for acid-fast bacilli (AFB) after 5 months of TB therapy to determine whether these patients were at higher risk of TB therapy failure or TB recurrence, which is determined by culture results. In the absence of TB culture results, WHO guidelines recommend classifying patients with positive AFB smears during the fifth month of TB therapy as having experienced TB therapy failure [2].

Methods. HIV-infected, ART-naive adults with a CD4$^+$ cell count >350 cells/μL and newly diagnosed pulmonary TB at the National Tuberculosis and Leprosy Programme clinic in Kampala, Uganda, were eligible for the Punctuated ART (PART) randomized, controlled trial. All participants received isoniazid, rifampicin, ethambutol, and pyrazinamide for 2 months and then isoniazid and rifampicin for 4 months. The intervention arm initiated 6 months of ART (with abacavir, zidovudine, and lamivudine) 2–4 weeks after starting TB therapy, while control-arm subjects received ART if their CD4$^+$ cell count was <250 cells/μL during follow-up. Institutional review boards in San Francisco, California, and Kampala, Uganda, approved this study.

Three sputum specimens were obtained for AFB smear and *Mycobacterium tuberculosis* (MTB) culture at baseline and 1, 2, 5, 12, and 18 months after initiating TB therapy. Smear- and culture-negative subjects were included if radiography and symptoms were consistent with TB.

TB therapy outcomes included time to conversion of smears and cultures to negative, TB therapy failure, TB recurrence, paradoxical reactions as defined by Narita et al [3], radiographic changes read by a blinded study radiologist at 1, 6, 12, and 18 months after initiation of TB therapy, and symptoms recorded during regular follow-up visits over 48 months. TB therapy failure was defined as MTB growth in sputum culture during the fifth month of TB therapy, independent of smear results [2]. Recurrence was defined as symptomatic or radiographic worsening, and new MTB growth in sputum culture for a patient with clinical improvement and negative culture results after completing TB therapy [2]. We hypothesized that ART would accelerate microbiologic, radiographic, and clinical TB therapy response and reduce TB therapy failures and TB recurrences.

Results. The intervention ($n = 109$) and control arms ($n = 114$) had similar baseline characteristics, aside from mediastinal adenopathy (Table 1). Median duration of follow-up was similar for both arms (22 months, interquartile range, 14–34 months).

High rates of HIV RNA suppression were achieved in the intervention arm after 6 months of ART, with 89 (86%) of 103 patients achieving a viral load <400 copies/mL. Median time

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Table 1. Baseline Clinical, Microbiologic, and Radiographic Characteristics of Patients with Human Immunodeficiency Virus Infection and Tuberculosis (TB) in Kampala, Uganda, by Study Arm

Characteristic	Control arm	Intervention arm	P[a]
Clinical characteristics			
Mean age, years	33	31	.22[b]
Male sex	70/114 (61)	56/109 (51)	.13
Median $CD4^+$ cell count, cells/μL	535	516	.51[c]
Median viral load, $\log_{10}$ copies/mL	4.6	4.6	.98[c]
Cough	114/114 (100)	107/109 (98)	.24
Purulent sputum	81/114 (71)	83/109 (76)	.39
Hemoptysis	11/114 (10)	11/109 (10)	.91
Sweats	85/114 (75)	69/109 (63)	.07
Fever	84/114 (74)	79/109 (73)	.84
Weight loss	91/114 (80)	81/109 (74)	.33
Microbiologic characteristics			
Positive for MTB on culture	98/113 (87)	98/108 (91)	0.35
Positive for AFB on smear	101/113 (89)	103/108 (95)	.13
Isoniazid resistance	4/92 (4)	3/95 (3)	.67
Multidrug resistance	0	0	
Baseline radiographic findings			
Upper lobe infiltrate	93/114 (82)	89/109 (82)	.99
Lower lobe infiltrate	84/114 (74)	83/109 (76)	.67
Fibrosis	14/114 (12)	9/109 (8)	.32
Cavitary disease	63/114 (55)	73/109 (67)	.07
Miliary disease	4/114 (4)	3/109 (3)	.99
Adenopathy	6/114 (5)	0	.03
Effusion	11/114 (10)	4/109 (4)	.08
Pleural thickening	5/114 (4)	3/109 (3)	.51
Extent of lung disease			
Normal	5/114 (4)	2/109 (2)	.39
Minimal	19/114 (17)	18/109 (16)	
Moderate	36/114 (32)	27/109 (25)	
Advanced	54/114 (47)	62/109 (57)	

NOTE. Data are proportion (%) of patients, unless otherwise indicated. AFB, acid-fast bacilli; MTB, *Mycobacterium tuberculosis*.

[a] Determined by use of the χ^2 test, unless otherwise indicated.
[b] Determined by use of the t test.
[c] Determined by use of the Wilcoxon rank sum test.

to conversion to negative MTB culture did not differ significantly in the intervention arm (38 days), compared with the control arm (29 days; by log-rank test, $P = .37$). Similarly, the median time to conversion to negative AFB smears did not differ significantly in the intervention arm (43 days), compared with the control arm (42 days; by log-rank test, $P = .27$; Figure 1). No TB therapy failures occurred in either arm. There were 3 TB recurrences in the intervention arm and 4 in the control arm ($P = .5$).

At completion of TB therapy, chest radiograph results were similar in both arms, although a greater proportion of lower lobe infiltrates was seen in the intervention arm, compared with the control arm (8% vs 0%; $P = .03$). This latter finding did not persist at month 12.

At month 6, the control arm had more patients with cough (43% vs 25%; $P = .007$), productive sputum (21% vs 9%; $P = .02$), dyspnea (6% vs 0%; $P = .02$), and rash (13% vs 3%; $P = .014$) than did the intervention arm. The most common causes of respiratory symptoms (41%) in the control arm were non-TB pneumonia and upper respiratory infections. By month 12, there were no significant symptomatic differences between study arms. No paradoxical reactions were observed.

Thirty (18%) of 165 participants in whom sputum specimens were obtained at month 5 were positive for AFB on smear (14 [18%] of 79 participants in the control arm and 16 [19%] of 86 participants in the intervention arm; $P = .88$); all had negative culture results. All 30 participants were positive on smear at baseline; 83% had grade 3+ bacilli on baseline smear, whereas

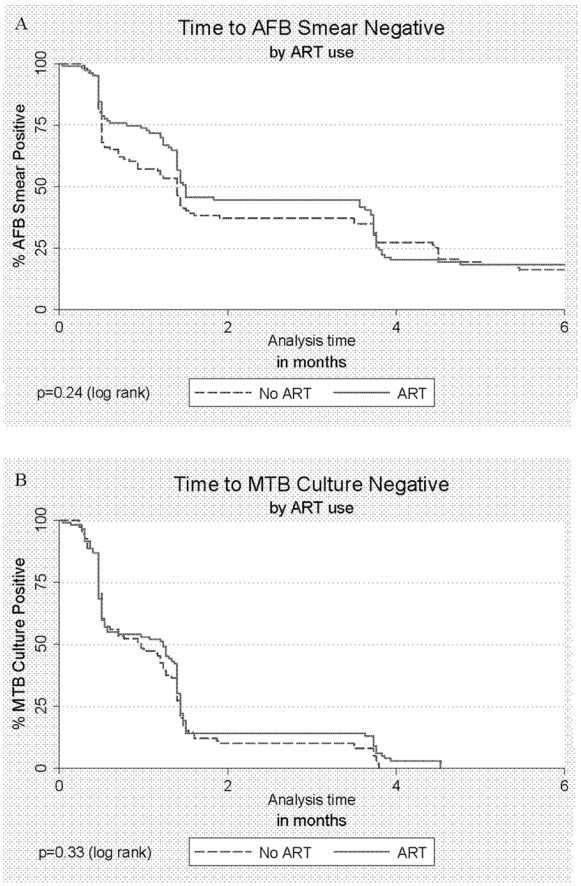

Figure 1. Time to conversion from positive to negative test results of acid-fast bacilli (AFB) smear (*A*) and *Mycobacterium tuberculosis* (MTB) culture (*B*) for HIV-infected patients with pulmonary TB who had a $CD4^+$ cell count >350 cells/μL (ie, for patients who received antiretroviral therapy [ART] during TB therapy and those who did not).

by the fifth month, 3% had grade 3+ bacilli on smear and 63% had grade 1+ bacilli on smear. None had baseline isoniazid resistance [4]. Of the 28 participants with smears performed at month 12 or 18, 25 were negative for AFB on smear, and 3 had recurrent TB. In univariate analysis, compared with participants whose smears were negative by month 5, participants whose smears were persistently positive were more likely to have had a positive culture result at baseline (100% vs 87%; $P = .02$), to have a baseline radiograph with cavitation (83% vs 60%; $P = .01$), pleural thickening (13% vs 2%; $P = .02$), and upper lobe infiltrates (97% vs 80%; $P = .02$), to be male (73% vs 48%; $P = .01$), and to have ever smoked tobacco (50% vs 26%; $P = .009$). In multivariate analysis, only cavitation (odds ratio, 3.3; 95% confidence interval, 1.1–10.1; $P = .03$) and pleural thickening (odds ratio, 7.2; 95% confidence interval, 1.5–34.6; $P = .01$) were independently associated with persistent smear positivity. There were no significant differences in culture conversion time, mean baseline $CD4^+$ cell count, or baseline symptoms between smear-positive and smear-negative groups at month 5. TB therapy failure rates and TB recurrence rates were similar between the groups.

Discussion. In a prospective, randomized controlled trial, we found that triple nucleoside ART does not accelerate microbiologic, clinical, or radiographic improvement during TB therapy in HIV-infected patients with TB and a high $CD4^+$ cell count. We found a high proportion of patients with persistent AFB in sputum smear late in TB therapy, despite sputum culture conversion, a finding associated with cavitation and pleural thickening on baseline chest radiograph but not ART use. Smear-positive, culture-negative status at month 5 was not associated with TB therapy failure or TB recurrence.

Few studies have evaluated the impact of ART on TB therapy response among coinfected patients with a high $CD4^+$ cell count. Given the central role of T cells in containing TB infection and developing TB-specific immunity [5], we hypothesized that ART-induced immune maintenance and recovery would accelerate the clinical, radiographic, and microbiologic responses to TB therapy. As new guidelines recommend ART in all HIV-infected patients with TB, the role of ART in TB therapy response in patients with a high $CD4^+$ cell count is particularly relevant [1].

Comparisons by HIV status in the pre-ART era suggested that HIV does not affect the likelihood of responding to TB therapy [6, 7], but these comparisons were limited by the competing risk of non-TB death at a low $CD4^+$ cell count. In a post-ART era study by Nahid et al [8], ART was associated with more rapid culture and smear conversion, although this observational study [8] may have been subject to selection bias and residual confounding on factors associated with ART use. Our randomized, controlled trial found no impact of ART on TB therapy response. Explanations of our findings include the possibility that the efficacy and speed of response to TB therapy are not dependent on T cell–mediated immunity. Alternatively, ART-induced T cell recovery with subsequent TB-specific immunity may take longer than 6 months to develop. It is possible that ART containing non–nucleoside reverse transcriptase inhibitors or protease inhibitors (regimens that are more virologically potent than triple nucleoside ART [9]) might accelerate response to TB therapy, although this seems unlikely given the high rates of virologic suppression achieved in the intervention arm. Although we found no benefit to ART in terms of TB therapy outcomes at high $CD4^+$ cell counts, multiple advantages to early ART initiation have been found, including decreased TB incidence with recovery of $CD4^+$ cell count to >500 cells/μL [10] and reduced all-cause mortality [11].

AFB smear positivity late in TB therapy occurred commonly in our study, despite TB culture clearance in all study participants and high rates of TB cure. HIV-infected patients with TB who have a high $CD4^+$ cell count tend to have a higher pulmonary bacillary load at diagnosis than do patients who

have a low $CD4^+$ cell count (<350 cells/μL) [12], and therefore they may be at higher risk for this phenomenon. Smear positivity with negative culture late in therapy is well described in HIV-uninfected patients and has been attributed to the persistence of nonviable MTB or to colonization with nontuberculous mycobacteria [13]. Patients in our study were not colonized with nontuberculous mycobacteria, which suggests the persistence of nonviable MTB. Similar to studies of HIV-uninfected patients with TB, we found persistent smear positivity to be associated with cavitary disease, likely reflecting slow clearance of MTB bacilli from the airway due to a high baseline bacillary burden [14]. Pleural thickening was also associated with late smear positivity, possibly due to greater parenchymal involvement in disease extending to the pleura.

In settings lacking MTB culture, WHO guidelines recommend classifying patients with positive AFB smear results during the fifth month of TB therapy as patients who experienced TB therapy failure [2]. Our results suggest that, in settings where smear alone is used for follow-up during TB therapy or where polymerase chain reaction testing may supplant culture during follow-up, there is significant potential for misclassification of patients as patients who experienced TB therapy failure despite a high likelihood of being cured at 6 months. Patients in our study received a standard 6-month course of TB therapy, which was guided by negative culture results. TB therapy was not extended, even in patients with positive smear results. There was no evidence of excess TB therapy failure or TB recurrence in these subjects who had close follow-up, although our study was underpowered to detect small differences between the groups. Further studies are needed to determine how to use current TB diagnostic methods to monitor treatment response in settings with limited access to TB culture.

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