ORIGINAL ARTICLE

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

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ABSTRACT

BACKGROUND

Antiretroviral therapy (ART) is indicated during tuberculosis treatment in patients infected with human immunodeficiency virus type 1 (HIV-1), but the timing for the initiation of ART when tuberculosis is diagnosed in patients with various levels of immune compromise is not known.

METHODS

We conducted an open-label, randomized study comparing earlier ART (within 2 weeks after the initiation of treatment for tuberculosis) with later ART (between 8 and 12 weeks after the initiation of treatment for tuberculosis) in HIV-1 infected patients with CD4+ T-cell counts of less than 250 per cubic millimeter and suspected tuberculosis. The primary end point was the proportion of patients who survived and did not have a new (previously undiagnosed) acquired immunodeficiency syndrome (AIDS)–defining illness at 48 weeks.

RESULTS

A total of 809 patients with a median baseline CD4+ T-cell count of 77 per cubic millimeter and an HIV-1 RNA level of 5.43 $\log_{10}$ copies per milliliter were enrolled. In the earlier-ART group, 12.9% of patients had a new AIDS-defining illness or died by 48 weeks, as compared with 16.1% in the later-ART group (95% confidence interval [CI], –1.8 to 8.1; P=0.45). Among patients with screening CD4+ T-cell counts of less than 50 per cubic millimeter, 15.5% of patients in the earlier-ART group versus 26.6% in the later-ART group had a new AIDS-defining illness or died (95% CI, 1.5 to 20.5; P=0.02). Tuberculosis-associated immune reconstitution inflammatory syndrome was more common with earlier ART than with later ART (11% vs. 5%, P=0.002). The rate of viral suppression at 48 weeks was 74% and did not differ between the groups (P=0.38).

CONCLUSIONS

Overall, earlier ART did not reduce the rate of new AIDS-defining illness and death, as compared with later ART. In persons with CD4+ T-cell counts of less than 50 per cubic millimeter, earlier ART was associated with a lower rate of new AIDS-defining illnesses and death. (Funded by the National Institutes of Health and others; ACTG A5221 ClinicalTrials.gov number, NCT00108862.)

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The treatment of patients with tuberculosis and newly identified infection with human immunodeficiency virus type 1 (HIV-1) is one of the most challenging aspects of HIV medicine. Antiretroviral therapy (ART) must be started during treatment for tuberculosis,[1,2] yet starting ART very early in the course of tuberculosis therapy increases the pill burden, the potential drug toxicity, and the risk of tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS).[3,4] For these reasons, programs, providers, and patients are reluctant to initiate ART during the intensive 8-week induction phase of tuberculosis therapy, when the pill burden and toxicity of tuberculosis medications are greatest. Conversely, delaying ART until after the completion of tuberculosis therapy increases morbidity and mortality associated with the acquired immunodeficiency syndrome (AIDS).[2] The timing of ART in patients who are receiving tuberculosis therapy is thus a critical question to address because more than a half-million persons die annually from HIV-associated tuberculosis.[5]

We designed a strategy trial to evaluate the timing of ART during tuberculosis therapy. Our trial included both patients with confirmed tuberculosis and those with suspected tuberculosis, since in clinical practice, the decision to start or delay ART must often be made before there is a definitive diagnosis of tuberculosis (a reflection of the current limitations of and access to tuberculosis diagnostics).[6] We sought to include patients from a wide geographic spectrum to maximize the generalizability of the findings and to inform policy.

METHODS

STUDY POPULATION

Patients were eligible for the study if they were 13 years of age or older, had HIV-1 infection with a CD4+ T-cell count of less than 250 per cubic millimeter, had not previously received ART, and had confirmed or probable tuberculosis. Confirmed tuberculosis was defined by the detection of acid-fast bacilli in a sputum smear or lymph-node specimen or a positive culture for *Mycobacterium tuberculosis* from sputum, a lymph node, or another sterile site. Probable tuberculosis required a clinician's assessment that signs and symptoms warranted empirical tuberculosis therapy. Patients were required to have received 1 to 14 days of a rifamycin-based treatment for tuberculosis. Entry criteria also included an absolute neutrophil count of 500 per cubic millimeter or more; a hemoglobin level of 7 g per deciliter or more; a platelet count of 50,000 per cubic millimeter or more; aspartate aminotransferase, alanine aminotransferase, and bilirubin levels that were no more than 5 times the upper limit of the normal range; a score of 20 or more on the Karnofsky performance scale (which ranges from 0 to 100, with higher scores indicating better performance); and no known or suspected multidrug-resistant or extensively drug-resistant tuberculosis. All participants provided written informed consent.

STUDY DESIGN

Our randomized, open-label, 48-week study compared earlier with later ART in persons with HIV-1 infection who were beginning to receive therapy for tuberculosis. Earlier ART was initiated within 2 weeks and later ART between 8 and 12 weeks after the start of tuberculosis treatment. Randomization was stratified according to screening CD4+ T-cell count (<50 or ≥50 per cubic millimeter) and was balanced according to site.

The ART regimen consisted of efavirenz at a dose of 600 mg daily (Stocrin, donated by Merck) and a fixed-dose combination of emtricitabine, at a dose of 200 mg daily, and tenofovir disoproxil fumarate, at a dose of 300 mg daily (Truvada, donated by Gilead Sciences). Substitutions of antiretroviral drugs were permitted for the management of toxic effects. Tuberculosis therapy was provided to the patients by the study sites according to the country's national tuberculosis guidelines. The protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board or ethics committee at each site. Companies donating drugs for this study did have the opportunity to review the manuscript, but they had no other role in study design, data accrual, or data analysis. The authors vouch for the accuracy and completeness of the data reported as well as the fidelity of the report to the study protocol. Full details of the study design are provided in the protocol.

Clinical and laboratory evaluations were conducted at entry; at weeks 4, 8, 12, and 16; and every 8 weeks thereafter for a total of 48 weeks. Plasma HIV-1 RNA (Roche Amplicor assay) and CD4+ T-cell counts were measured at Division of AIDS (DAIDS)–certified laboratories. Adverse events were graded with the use of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, as recommended by the National Institute of Allergy and Infectious Diseases (NIAID).[7]

END POINTS

The primary study end point was the proportion of participants who survived to week 48 without a new (previously undiagnosed) AIDS-defining illness. An independent reviewer who was unaware of the study-group assignments assessed new AIDS-defining events on the basis of standardized definitions of the AIDS Clinical Trials Group. The cause of death was reviewed by the study-team member who was unaware of study-group assignments. A reviewer who was unaware of the study-group assignments confirmed tuberculosis-associated IRIS cases on the basis of at least one major or two minor clinical criteria.[8] Concurrent ART was not required for a patient to be classified as having tuberculosis-associated IRIS.[3]

STATISTICAL ANALYSIS

The National Institutes of Health funded the study and provided study oversight. Since this was a strategy study, all participants who met clinical eligibility criteria were included in the analyses. Participants were followed for up to 48 weeks, regardless of whether or not they started ART as scheduled. We determined that a sample of 400 patients per group would provide 90% power (at a two-sided alpha level of 0.05) to detect a 40% reduction in the rate of treatment failure with later ART versus earlier ART (from 25% to 15%), with adjustment for a 10% rate of loss to follow-up and interim analyses. Treatment assignments were generated by a central computer with the use of permuted blocks within strata.

Estimated proportions of patients who survived without a new AIDS event at 48 weeks and failure-time plots were calculated with the use of the Kaplan–Meier method.[9] Failure was defined at the first qualifying event. Tests and confidence intervals that were stratified according to the screening CD4+ T-cell count category, as well as interactions with respect to the primary end point, were calculated by weighting by the inverse of the Greenwood's variance in each CD4+ T-cell count stratum.[10] Two prespecified subgroup analyses of the primary end point according to CD4+ T-cell count strata and level of diagnostic certainty with regard to tuberculosis (probable or confirmed) were performed and are reported here. A post hoc subgroup analysis of the primary end point according to body-mass index (BMI) and a post hoc analysis of mortality were performed; the BMI results are reported here. These analyses were tested in the same manner as that described above. Unstratified log-rank, Fisher's exact, Pearson chi-square, and Wilcoxon tests were used to assess between-group differences in secondary end points.

An NIAID data and safety monitoring board monitored the trial annually. Prespecified interim reviews of efficacy were performed by means of the O'Brien–Fleming method[11] with a Lan–DeMets spending function.[12] Two efficacy analyses were presented to the data and safety monitoring board. With adjustment for these analyses, a P value of less than 0.05 for the primary end point was considered to indicate statistical significance. Confidence intervals for the primary end point were similarly adjusted.

RESULTS

PATIENTS

From September 2006 through August 2009, a total of 809 patients were enrolled (Fig. 1) at 26 clinical-research sites in four continents (Table 1). Three patients who were medically ineligible were removed from the study and excluded from the analysis. The median baseline CD4+ T-cell count was 77 per cubic millimeter (interquartile range, 36 to 145); 46% of patients had confirmed tuberculosis. Among 120 patients who underwent baseline testing for susceptibility to tuberculosis drugs, 8 had isoniazid resistance, 5 had multidrug-resistant tuberculosis, and 3 had single-drug resistance to rifampin, pyrazinamide, or ethambutol. A total of 94% of the patients received trimethoprim–sulfamethoxazole prophylaxis.

PRIMARY END POINT

There were 26 new AIDS-defining illnesses and 26 deaths in the earlier-ART group and 37 new AIDS-defining illnesses and 27 deaths in the later-ART group (Table 2), with no significant difference between the groups with respect to the rates of this combined outcome (12.9% vs. 16.1%; 95% confidence interval [CI], –1.8 to 8.1; P=0.45, stratified according to the screening CD4+ T-cell count) (Fig. 2). In a prespecified subgroup analysis of the primary end point, among patients with CD4+ T-cell counts of less than 50 per cubic millimeter, the rate of new AIDS-defining illness or death was significantly lower in the earlier-ART

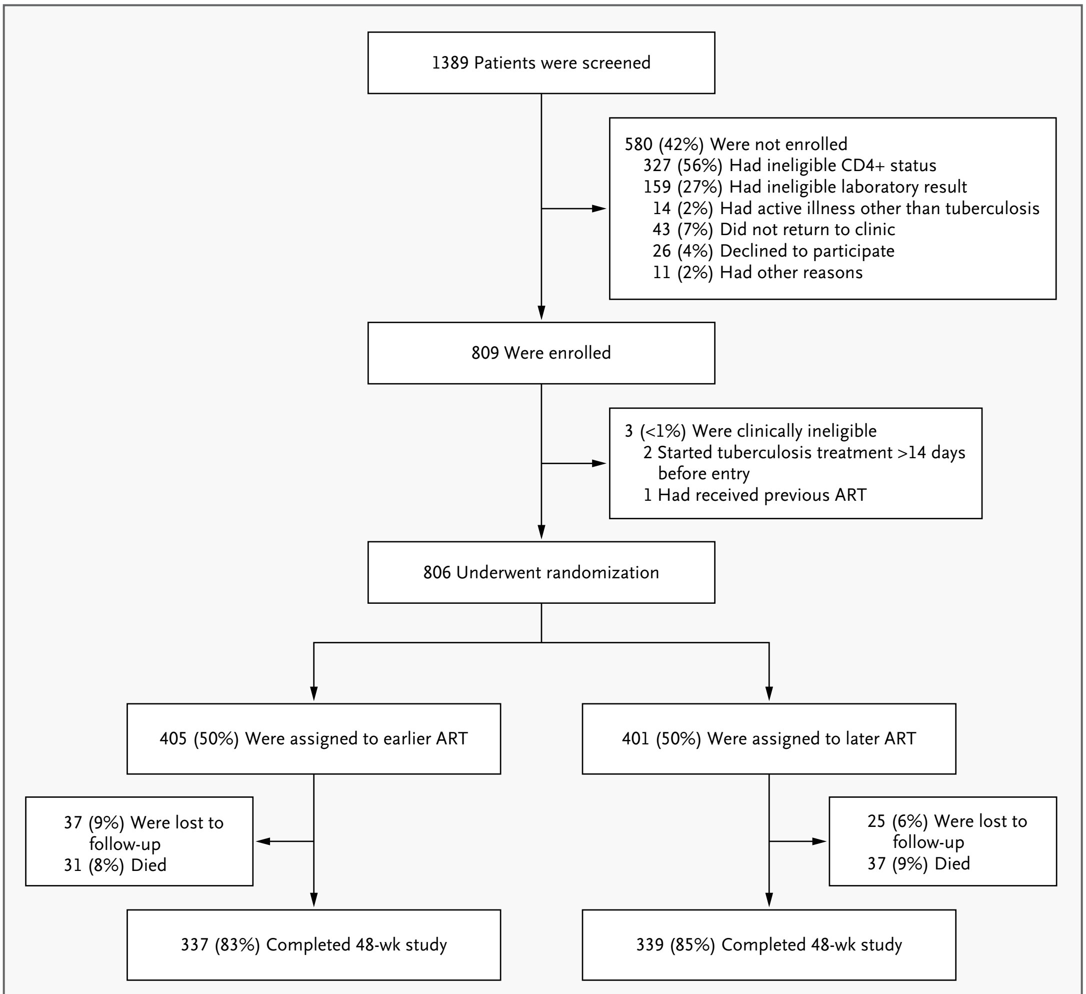


Figure 1. Screening, Enrollment, and Follow-up of Study Patients.
ART denotes antiretroviral therapy.

group than in the later-ART group (15.5% vs. 26.6%; 95% CI, 1.5 to 20.5; P=0.02); there was no significant difference between the groups among patients with CD4+ T-cell counts of 50 or more per cubic millimeter (P=0.67). There was no interaction between the CD4+ T-cell count stratum and treatment group (P=0.13). When the analysis was performed within subgroups defined according to confirmed or probable tuberculosis, there were no significant differences between the treatment groups (P=0.21 and 0.35, respectively, stratified according to the screening CD4+ T-cell count); results according to each CD4+ T-cell count stratum within these subgroups were consistent with the primary result. In patients with a baseline BMI (the weight in kilograms divided by the square of the height in meters) of 18.5 or less, there were fewer events in the earlier-ART group than in the later-ART group (P=0.06, stratified according to the CD4+ T-cell count). This result was largely driven by the significant reduction in the primary end point among patients in the lower stratum of the CD4+ T-cell count who received earlier ART (15.2%, vs. 38.2% among patients in the same stratum who received later ART; 95% CI, 8.0 to 37.8; P=0.003).

The most common AIDS-defining illnesses were extrapulmonary cryptococcal disease, esophageal candidiasis, and Kaposi's sarcoma (see Table 7 in the Supplementary Appendix, available at NEJM.org). Overall, there were 31 deaths in the earlier-ART group and 37 deaths in the later-ART group. A total of 21 of 31 deaths (68%) in

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Earlier ART (N=405)	Later ART (N=401)	All Patients (N=806)
Continent — no. (%)			
Africa	275 (68)	279 (70)	554 (69)
Asia	29 (7)	23 (6)	52 (6)
North America	21 (5)	18 (4)	39 (5)
South America	80 (20)	81 (20)	161 (20)
Male sex — no. (%)	266 (66)	235 (59)	501 (62)
Age at enrollment — yr			
Median	34	34	34
Interquartile range	29–40	29–42	29–41
Tuberculosis — no. (%)			
Confirmed	193 (48)	181 (45)	374 (46)
Probable	208 (51)	218 (54)	426 (53)
Not tuberculosis	4 (1)	2 (<1)	6 (1)
CD4+ T-cell count/mm^3			
Median	70	82	77
Interquartile range	34–146	40–144	36–145
HIV-1 RNA—$\log_{10}$ copies/ml			
Median	5.39	5.50	5.43
Interquartile range	4.94–5.79	5.03–5.79	5.00–5.79
Prior AIDS diagnosis — no. (%)	26 (6)	29 (7)	55 (7)
Body-mass index			
Median	19.1	19.4	19.2
Interquartile range	17.3–21.1	17.7–21.8	17.5–21.4
Initial ART regimen of efavirenz, tenofovir disoproxil fumarate, emtricitabine — no./total no. (%)†	394/403 (98)	368/380 (97)	762/783 (97)
Interval between start of tuberculosis therapy and start of ART — days			
Median	10	70	
Interquartile range	7–12	66–75	

* The time to the initiation of ART differed between the groups according to the design, and accrual within the CD4 strata and site was controlled according to the randomization scheme. All other factors shown here did not differ between the groups. The body-mass index is the weight in kilograms divided by the square of the height in meters. AIDS denotes acquired immunodeficiency syndrome, ART antiretroviral therapy, and HIV-1 human immunodeficiency virus type 1.
† Percentages are based on the number of patients who started ART.

the earlier-ART group and 21 of 37 deaths (57%) in the later-ART group were attributed to HIV-related disease, including progression of tuberculosis. Of these 42 deaths, 21 were attributed to HIV-related diseases other than tuberculosis, including bacterial infection or sepsis (in 10 patients), cryptococcal meningitis (in 5 patients), cytomegalovirus disease (in 2 patients), *M. avium* complex (in 2 patients), toxoplasmosis (in 1 patient), and lymphoma (in 1 patient). Among the 21 deaths attributed to tuberculosis, there were 14 in the earlier-ART group and 7 in the later-ART group (P=0.18). Thirteen of these deaths were ascribed to pulmonary tuberculosis, and 8 deaths were ascribed to extrapulmonary tuberculosis, including 4 cases of reported tuberculosis affecting the central nervous system.

In a sensitivity analysis that also included 23 patients with a single episode of bacterial pneumonia as the primary end point, the between-group difference in the rate of the primary end point remained nonsignificant (14.6% in the earlier-ART group and 19.7% in the later-ART group; 95% CI, −0.2 to 10.4; P=0.14, stratified

Table 2. Rates of New AIDS-Defining Illness or Death at 48 Weeks, According to CD4+ T-Cell Count.

Study Population and CD4+ T-Cell Count	No. of Patients	AIDS or Death		95% CI for Difference in Proportions	P Value
		Earlier ART	Later ART		
		percent			
All patients	806	12.9	16.1	−1.8 to 8.1	0.45*
<50 cells/mm³	285	15.5	26.6	1.5 to 20.5	0.02
≥50 cells/mm³	521	11.5	10.3	−6.7 to 4.3	0.67
Confirmed tuberculosis at study entry	374	13.8	19.7	−1.8 to 13.6	0.21*
<50 cells/mm³	151	17.9	31.4	−0.4 to 27.3	0.06
≥50 cells/mm³	223	10.8	12.1	−7.3 to 9.8	0.77
Suspected tuberculosis at study entry	432	15.4	19.7	−3.0 to 11.7	0.35*
<50 cells/mm³	134	14.1	30.5	2.5 to 30.4	0.02
≥50 cells/mm³	298	15.9	14.5	−9.8 to 7.1	0.75
Low BMI (≤18.5) at study entry	332	16.3	26.5	1.2 to 19.2	0.06*
<50 cells/mm³	130	15.2	38.2	8.0 to 37.8	0.003
≥50 cells/mm³	202	16.9	17.8	−9.9 to 11.6	0.88

* This P value was stratified according to the screening CD4+ T-cell count (<50 or ≥50 per cubic millimeter).

according to the CD4+ T-cell count). However, the between-group difference among patients with a CD4+ T-cell count of less than 50 per cubic millimeter was significant (16.2% vs. 31.0%; 95% CI, 4.9 to 24.6; P=0.003).

HIV RNA AND IMMUNE RESPONSE TO ART

Suppression of plasma HIV RNA to less than 400 copies per milliliter was achieved in 95% of the 663 patients for whom data were available at the end of 48 weeks (Table 3). Overall, the rate of viral suppression at the end of 48 weeks was 74% (596 of 806 patients), with no significant difference between the treatment groups (P=0.38). In 35 patients, the definition of virologic failure was met, with no significant between-group difference. The median change in the CD4+ T-cell count at the end of 48 weeks was 156 per cubic millimeter in 666 patients and did not differ significantly between the groups (P=0.46).

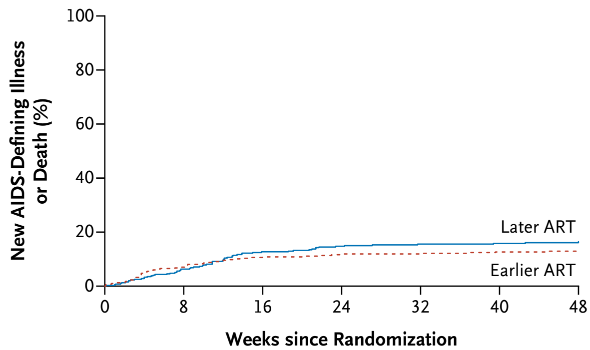
TUBERCULOSIS-ASSOCIATED IRIS

A total of 62 of the 806 patients (8%) met the criteria for tuberculosis-associated IRIS: 43 patients in the earlier-ART group (11%) and 19 in the later-ART group (5%) (P=0.002) at a median of 4.6 and 11.7 weeks from the start of tuberculosis treatment, respectively (P<0.001). The median time from the start of antiretroviral therapy to the development of tuberculosis-associated IRIS was 21 days (interquartile range, 10 to 59) in the earlier-ART group and 15 days (interquartile range, 7 to 23) in the later-ART group. Four of the IRIS cases in the later-ART group developed before the initiation of antiretroviral therapy. The proportion of patients with grade 3 or 4 adverse events attributed to tuberculosis-associated IRIS was 40% in the earlier-ART group and 47% in the later-ART group (P=0.80). The median time to resolution of symptoms was 75 days in the earlier-ART group versus 69 days in the later-ART group. Prednisone was used in 29 of the 62 patients for a median duration of 15 days. There were no deaths attributed to tuberculosis-associated IRIS among the patients who were classified as having tuberculosis-associated IRIS.

ADVERSE EVENTS

Grade 3 or 4 toxic effects were reported in 18% of patients and were similar in the two study groups (Table 4). Constitutional symptoms, including fever and weight loss, were the most common grade 3 or 4 events, occurring in 8% of patients. Grade 3 or 4 laboratory abnormalities were reported in 46% of patients and were similar in the two study groups; the notable exceptions were neutropenia (in 36 patients in the earlier-ART group vs. 69 patients in the later-ART group, P=0.001) and thrombocytopenia (3 vs. 13 patients, P=0.01). Twenty-one of 783 patients (14

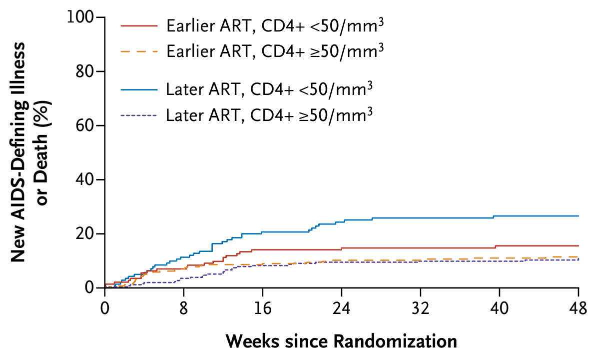
A



No. at Risk

Earlier therapy	405	368	346	341	335	324	226
Later therapy	401	371	342	329	325	318	218

B



No. at Risk

Earlier therapy							
CD4+ $<50/mm^3$	144	132	121	121	118	114	74
CD4+ $\geq 50/mm^3$	261	236	225	220	217	210	152
Later therapy							
CD4+ $<50/mm^3$	141	125	110	103	101	98	69
CD4+ $\geq 50/mm^3$	260	246	232	226	224	220	149

Figure 2. Time to New AIDS-Defining Illness or Death.
Shown are the times to the end point of a new AIDS-defining illness or death for the entire study population (Panel A) and for the study population according to CD4+ T-cell count (Panel B).

in the earlier-ART group and 7 in the later-ART group) who started ART switched regimens. A total of 56% of patients completed tuberculosis treatment without a modification or an interruption in the regimen, with no significant difference between the groups.

DISCUSSION

Our study showed that ART can be safely administered soon after the initiation of tuberculosis treatment and that the urgency of starting ART earlier after the initiation of tuberculosis therapy depends on the immune status of the patient. Among patients with CD4+ T-cell counts below 50 per cubic millimeter, new AIDS-defining illnesses and deaths were reduced by 11.1 percentage points, from 26.6% to 15.5%, in the group of patients who started ART 2 weeks after the initiation of tuberculosis treatment, a 41.7% reduction as compared with those who started 8 to 12 weeks after the initiation of tuberculosis therapy. That this short delay in the initiation of ART in patients with low CD4+ T-cell counts would have such an effect on the rate of new AIDS-defining illnesses and death highlights the vulnerability of immunosuppressed patients with tuberculosis to these complications and the remarkable capacity of ART to abrogate them rapidly.

Our study showed that among patients with CD4+ T-cell counts of 50 per cubic millimeter or higher, waiting 8 to 12 weeks after the initiation of tuberculosis therapy to start ART did not confer any increase in the risk of a new AIDS-defining illness or death and was associated with fewer cases of IRIS. For several reasons, including the risk of tuberculosis-associated IRIS, this brief delay in starting ART may simplify the management of tuberculosis, although there were cases of IRIS in the later-ART group. Our findings should not be interpreted as indicating that there is no urgency in starting ART in this group of patients; indeed, delaying ART until after completion of tuberculosis therapy was associated with increased mortality in an earlier randomized study.[2]

The results of this trial complement and extend findings from concurrent randomized studies of ART involving HIV-1–infected persons with tuberculosis. Elsewhere in this issue of the *Journal*, Blanc et al.[13] report on the results of the Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA) study (ClinicalTrials.gov number, NCT00226434). The rate of death in the CAMELIA study (median baseline CD4+ T-cell count, 25 per cubic millimeter [interquartile range, 10 to 56]) and the rates of death or AIDS-defining illness among patients with a low CD4+ T-cell count (<50 per cubic millimeter) in our study and in the Starting Antiretroviral Therapy at Three Points in Tuberculosis (ClinicalTrials.gov number, NCT00398996) study, reported on by Abdool Karim et al.[14] in this issue of the *Journal*, were all significantly reduced with earlier versus later ART. Our inclusion of patients from four continents and cases of either confirmed or probable tuberculosis also extends the generalizability of prior studies.

Table 3. HIV RNA Level and Immune Response to Antiretroviral Therapy.

Outcome	Wk 8	Wk 16	Wk 24	Wk 32	Wk 48
HIV-1 RNA <400 copies/ml — no./total no. (%)					
Earlier ART	273/370 (74)	314/361 (87)	320/355 (90)	312/349 (89)	293/331 (89)
Later ART	4/380 (1)	237/365 (65)	295/349 (85)	313/347 (90)	301/332 (91)
CD4+ T-cell count					
Earlier ART					
No. of patients	368	357	350	346	333
Median — cells/mm³	200	207	218	219	246
Interquartile range — cells/mm³	121 to 275	134 to 279	145 to 294	154 to 305	169 to 352
Later ART					
No. of patients	379	364	347	343	333
Median — cells/mm³	77	193	207	221	250
Interquartile range — cells/mm³	34 to 140	113 to 289	130 to 296	150 to 308	173 to 343
Change from baseline in CD4+ T-cell count					
Earlier ART					
No. of patients	368	357	350	346	333
Median — cells/mm³	93	107	124	132	160
Interquartile range — cells/mm³	48 to 172	5 to 168	72 to 189	77 to 198	91 to 240
Later ART					
No. of patients	379	364	347	343	333
Median — cells/mm³	−2	95	104	124	151
Interquartile range — cells/mm³	−23 to 14	43 to 165	60 to 173	71 to 204	94 to 228

Clinicians are often hesitant to initiate ART because of potential drug toxicity and laboratory abnormalities that may occur when ART and tuberculosis therapy are started at approximately the same time. Overall, there was no significant difference in these events between the strategies of earlier and later ART. The frequency of neutropenia and of thrombocytopenia was higher in the later-ART group than in the earlier-ART group. Although the explanation for this difference is probably multifactorial, earlier ART may have had a more rapid effect in reversing the bone marrow suppression that is characteristic of untreated HIV disease.

The rate of tuberculosis-associated IRIS was higher in the earlier-ART group than in the later-ART group, a finding that is consistent with the results of previous studies.[8] However, the more frequent and earlier occurrence of these events did not lead to worse overall outcomes. Prednisone was used to alleviate symptoms in about half the patients with tuberculosis-associated IRIS in our study. The use of prednisone to reduce the symptoms of tuberculosis-associated IRIS without increasing susceptibility to and masking other AIDS complications is an area of active study.[15]

Assessment of ART strategies must take into account the rate of plasma HIV-1 RNA suppression and the immune response. Starting ART early could jeopardize adherence to treatment and lead to increased rates of virologic failure, development of viral resistance, and worsening of the immune response. Patients treated simultaneously for tuberculosis and HIV-1 infection have an extremely high pill burden, and side effects of the antimicrobial agents overlap not only with each other but also with the clinical manifestations of tuberculosis. Thus, it is reassuring that even though the earlier start of ART imposes the additional burden of having to adhere to a complex treatment regimen, similar rates of viral suppression at 48 weeks were achieved among study participants in the earlier-ART group and those in whom ART was delayed until at least 8 weeks after the initiation of tuberculosis treatment. Similar results were observed in ACTG A5164 (ClinicalTrials.gov number, NCT00055120), an ART

Table 4. Grade 3 or 4 Clinical Events or Laboratory Abnormalities.*

Event	Earlier ART (N=405)	Later ART (N=401)	Total (N=806)
		number of patients (percent)	
Clinical event			
Constitutional	31 (8)	31 (8)	62 (8)
Respiratory	17 (4)	16 (4)	33 (4)
Cardiac or circulatory	11 (3)	7 (2)	18 (2)
Gastrointestinal	17 (4)	20 (5)	37 (5)
Cutaneous	11 (3)	11 (3)	22 (3)
Neurologic	22 (5)	28 (7)	50 (6)
Laboratory abnormality			
Absolute neutrophil count $<750/mm^3$†	36 (9)	69 (17)	105 (13)
Hemoglobin <7.5g/dl	28 (7)	22 (5)	50 (6)
Platelet count $<50,000/mm^3$‡	3 (1)	13 (3)	16 (2)
Aminotransferase >5× ULN§	26 (6)	41 (10)	67 (8)
Creatinine >1.9× ULN	12 (3)	7 (2)	19 (2)
Any laboratory abnormality	65 (16)	55 (14)	120 (15)
Any grade 3 or 4 adverse event	177 (44)	190 (47)	367 (46)

* ULN denotes upper limit of the normal range.
† P=0.001.
‡ P=0.01.
§ Patients with elevations of aspartate aminotransferase, alanine aminotransferase, or both were included in this category.

strategy study involving patients with AIDS conditions other than tuberculosis.[16]

Patients with known drug-resistant tuberculosis were ineligible for our study; thus, our results may not be applicable to this population.[17] In addition, our study does not provide definitive guidance for the care of patients with tuberculosis-associated meningitis, in whom IRIS can lead to inflammation in the central nervous system. A recent randomized study of adults with tuberculosis-associated meningitis in Vietnam showed very high mortality in both treatment groups and no benefit of earlier versus later ART.[18] These exceptions notwithstanding, our study shows that it is feasible and safe to start ART within 2 weeks after the initiation of tuberculosis treatment and that for patients with CD4+ T-cell counts of less than 50 per cubic millimeter, this timing of treatment significantly reduces morbidity and mortality.

Applying the findings of this study to the clinical setting will require a concerted and coordinated effort on the part of tuberculosis and HIV programs worldwide. Prompt HIV testing in patients with tuberculosis is critical for the application of our findings.[19] Although progress is visible on this front, less than half of patients in sub-Saharan Africa who presented to tuberculosis-control programs in 2008 underwent HIV testing.[5] Implementation of these findings also means that ART must be available at the tuberculosis clinic or there must be a seamless and prompt referral of patients from the tuberculosis clinic to an HIV clinic for rapid initiation of ART.[20,21] The time requirements for counseling regarding adherence to HIV and ART before the initiation of ART will need to be balanced with the substantial risk of illness and death associated with delayed treatment. Training for identification and treatment of tuberculosis-associated IRIS may need to be increased. Implementation studies that identify barriers to adaptation of the clinical practice of earlier ART for patients with low CD4+ T-cell counts and newly diagnosed tuberculosis are warranted.

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Appendix

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References

1. Sterling TR, Pham PA, Chaisson RE. HIV infection-related tuberculosis: clinical manifestations and treatment. Clin Infect Dis 2010;50:Suppl 3:S223-S230.

2. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med 2010;362:697-706.

3. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax 2004;59:704-7.

4. Burman W, Weis S, Vernon A, et al. Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. Int J Tuberc Lung Dis 2007; 11:1282-9.

5. Global tuberculosis control: a short update to the 2009 report. Geneva: World Health Organization, 2009. (http:/whqlibdoc.who.int/publications/2009/9789241598866_eng.pdf.)

6. Pai M, Minion J, Sohn H, Zwerling A, Perkins MD. Novel and improved technologies for tuberculosis diagnosis: progress and challenges. Clin Chest Med 2009;30: 701-16.

7. Division of AIDS table for grading the severity of adult and pediatric adverse events. Bethesda, MD: National Institute of Allergy and Infectious Diseases, 2004. (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/daidsaegradingtable.pdf.)

8. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis 2008;8:516-23.

9. Kaplan E, Meier P. Nonparametric estimation of incomplete observations. J Am Stat Assoc 1958;53:457-81.

10. Kalbfleisch J, Prentice R. The statistical analysis of failure time data. New York: John Wiley, 1980.

11. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.

12. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.

13. Blanc F-X, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med 2011;365:1471-81.

14. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011;365:1492-501.

15. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS 2010;24:2381-90.

16. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One 2009;4(5): e5575.

17. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet 2010;375:1798-807.

18. Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. Clin Infect Dis 2011;52:1374-83.

19. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. Clin Infect Dis 2010;50:Suppl 3:S201-S207.

20. Havlir DV, Getahun H, Sanne I, Nunn P. Opportunities and challenges for HIV care in overlapping HIV and TB epidemics. JAMA 2008;300:423-30.

21. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. Clin Infect Dis 2010;50:Suppl 3:S238-S244.