ORIGINAL ARTICLE

Integration of Antiretroviral Therapy with Tuberculosis Treatment

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ABSTRACT

BACKGROUND

We previously reported that integrating antiretroviral therapy (ART) with tuberculosis treatment reduces mortality. However, the timing for the initiation of ART during tuberculosis treatment remains unresolved.

METHODS

We conducted a three-group, open-label, randomized, controlled trial in South Africa involving 642 ambulatory patients, all with tuberculosis (confirmed by a positive sputum smear for acid-fast bacilli), human immunodeficiency virus infection, and a CD4+ T-cell count of less than 500 per cubic millimeter. Findings in the earlier-ART group (ART initiated within 4 weeks after the start of tuberculosis treatment, 214 patients) and later-ART group (ART initiated during the first 4 weeks of the continuation phase of tuberculosis treatment, 215 patients) are presented here.

RESULTS

At baseline, the median CD4+ T-cell count was 150 per cubic millimeter, and the median viral load was 161,000 copies per milliliter, with no significant differences between the two groups. The incidence rate of the acquired immunodeficiency syndrome (AIDS) or death was 6.9 cases per 100 person-years in the earlier-ART group (18 cases) as compared with 7.8 per 100 person-years in the later-ART group (19 cases) (incidence-rate ratio, 0.89; 95% confidence interval [CI], 0.44 to 1.79; P=0.73). However, among patients with CD4+ T-cell counts of less than 50 per cubic millimeter, the incidence rates of AIDS or death were 8.5 and 26.3 cases per 100 person-years, respectively (incidence-rate ratio, 0.32; 95% CI, 0.07 to 1.13; P=0.06). The incidence rates of the immune reconstitution inflammatory syndrome (IRIS) were 20.1 and 7.7 cases per 100 person-years, respectively (incidence-rate ratio, 2.62; 95% CI, 1.48 to 4.82; P<0.001). Adverse events requiring a switching of antiretroviral drugs occurred in 10 patients in the earlier-ART group and 1 patient in the later-ART group (P=0.006).

CONCLUSIONS

Early initiation of ART in patients with CD4+ T-cell counts of less than 50 per cubic millimeter increased AIDS-free survival. Deferral of the initiation of ART to the first 4 weeks of the continuation phase of tuberculosis therapy in those with higher CD4+ T-cell counts reduced the risks of IRIS and other adverse events related to ART without increasing the risk of AIDS or death. (Funded by the U.S. President's Emergency Plan for AIDS Relief and others; SAPIT ClinicalTrials.gov number, NCT00398996.)

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In patients who have infection with the human immunodeficiency virus (HIV) and tuberculosis, antiretroviral therapy (ART) may be initiated at the same time as or soon after the initiation of tuberculosis treatment. However, antiretroviral agents are often deferred until after the intensive phase of tuberculosis treatment because of concern about the immune reconstitution inflammatory syndrome (IRIS),[1,2] a high pill burden, and overlapping side effects[3] when three antiretroviral agents are added to the standard four antituberculosis drugs. These challenges may result in interruption or discontinuation of treatment for the acquired immunodeficiency syndrome (AIDS) or tuberculosis, which can lead to drug resistance and potentially limit future therapeutic options,[4,5] but the disadvantages must be weighed against the risk of increased mortality early in the treatment of tuberculosis.

The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial[6] was designed to determine the clinical consequences of the time to the start of ART in patients with HIV infection and tuberculosis. We previously reported that integrating ART with tuberculosis treatment reduces mortality.[6] Here, we report on the initiation of ART at two points during tuberculosis treatment.

Methods

Study Design, Patients, and Procedures

We conducted a prospective, open-label, randomized trial in South Africa. A total of 642 ambulatory patients with both pulmonary tuberculosis and HIV infection, 18 years of age or older, were enrolled after providing written informed consent.

The diagnosis of pulmonary tuberculosis was confirmed by a positive sputum smear for acid-fast bacilli. HIV infection was confirmed by two rapid screening tests for HIV. All patients had a CD4+ T-cell count of less than 500 per cubic millimeter at screening and were started on a standard tuberculosis treatment regimen.[7] All patients with a first episode of tuberculosis were treated with a fixed combination of rifampin, isoniazid, ethambutol, and pyrazinamide, with doses determined according to pretreatment weight, for 2 months (intensive phase) and a subsequent fixed combination of isoniazid and rifampicin for 4 months (continuation phase). Patients who had previously received treatment for tuberculosis received a 60-day intensive regimen that included streptomycin, followed by a 100-day continuation regimen.

The once-daily ART regimen consisted of enteric-coated didanosine (250 mg if the patient's weight was <60 kg and 400 mg if the weight was ≥60 kg), lamivudine (300 mg), and efavirenz (600 mg). Adherence to ART was assessed monthly by means of pill counts. Notwithstanding the study-group assignments, patients could be started on ART at any time at the discretion of the study clinicians or the patients' primary care physicians. Details of the study design and procedures have been described previously[6] and are provided in the protocol and Supplementary Appendix, available with the full text of this article at NEJM.org.

The outcome of the sequential-therapy group (ART initiated after the completion of tuberculosis treatment) has been reported previously.[6] The analysis reported here includes complete follow-up data on the 214 patients in the early integrated-therapy group (ART initiated within 4 weeks after the start of tuberculosis treatment) and the 215 patients in the late integrated-therapy group (ART initiated within 4 weeks after completion of the intensive phase of tuberculosis treatment).

Study Oversight

The trial was approved by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal and by the Medicines Control Council of the South African government. Study data were reviewed periodically by a data and safety monitoring committee. All authors vouch for the completeness and accuracy of the data and analyses presented.

Statistical Analysis

All analyses were performed in the intention-to-treat population. The primary outcome, the incidence rate of AIDS or death, was analyzed with the use of Kaplan–Meier curves. The duration of time in the study was calculated as the time from randomization to death or AIDS-defining illness, withdrawal from the study, or 18 months after randomization, whichever occurred first. Poisson approximations were used to calculate confidence intervals for the incidence-rate ratios. Cox proportional-hazards regression was used to adjust for confounding variables. Fisher's exact test was used for the analysis of categorical data, and unpaired t-tests or the Wilcoxon two-sample test was used

for the analysis of continuous data. Interactions between therapy group and CD4+ T-cell count were evaluated by fitting a proportional-hazards model with therapy group, CD4+ T-cell count, and the interaction between therapy group and CD4+ T-cell count.

RESULTS

STUDY PARTICIPANTS

A total of 429 patients were enrolled in the two integrated-therapy groups: 214 were randomly assigned to receive early integrated therapy (hereafter referred to as the earlier-ART group), and 215 were assigned to receive late integrated therapy (hereafter referred to as the later-ART group). At baseline, the two groups had similar demographic and clinical characteristics (Table 1). The median CD4+ T-cell count was 150 per cubic millimeter, and the median viral load was 161,000 copies per milliliter. The median duration of follow-up in the trial was 17.7 months (interquartile range, 14.0 to 17.8). At study completion, the retention rates were 76.9% and 71.5% in the earlier-ART and later-ART groups, respectively (information on retention and causes of death is provided in the Supplementary Appendix).

INITIATION OF ART

Among patients who completed tuberculosis therapy, the median treatment duration was 210 days in the earlier-ART group (207 participants) and 203 days in the later-ART group (210 participants). A total of 92.5% of the patients in the earlier-ART group (198 of 214) and 76.3% in the later-ART group (164 of 215) started ART during the study (P<0.001). The longer period from randomization to the initiation of ART in the later-ART group meant that more patients in this group were lost to follow-up, withdrew, or died before the start of ART, as compared with the earlier-ART group (Fig. 1). However, there were no significant differences between the earlier-ART and later-ART groups in the overall rates of loss to follow-up (12.1% [26 of 214] and 15.8% [34 of 215], P=0.33) and withdrawal (9.3% [20 of 214] and 10.7% [23 of 215], P=0.75).

The 198 patients in the earlier-ART group who started ART did so at a median of 21 days (interquartile range, 15 to 29) after the initiation of tuberculosis therapy. Of the 33 patients who started ART after the 4-week window, 9 missed the study-clinic visit for the initiation of ART, 8 had abnormal liver function, 2 had other laboratory abnormalities, 4 declined ART, and 10 had clinical conditions that precluded ART initiation.

The 164 patients in the later-ART group who started ART did so at a median of 97 days (interquartile range, 77 to 126) after the initiation of tuberculosis therapy. One patient started ART during the intensive phase of tuberculosis treatment. Of the 47 patients who started ART more than 4 weeks after completion of the intensive phase of tuberculosis treatment, 29 missed the study-clinic visit for the initiation of ART, 1 had abnormal liver function, 6 declined ART, and 11 had clinical conditions that precluded ART initiation.

INCIDENCE RATES OF AIDS OR DEATH

The incidence rate of AIDS or death was 6.9 cases per 100 person-years in the earlier-ART group (18 cases) as compared with 7.8 per 100 person-years in the later-ART group (19 cases) (incidence-rate ratio, 0.89; 95% confidence interval [CI], 0.44 to 1.79; P=0.73). After adjustment for baseline World Health Organization (WHO) disease stage (stage 4 vs. stage 3), age, sex, history of tuberculosis (yes or no), presence or absence of extrapulmonary tuberculosis, and baseline CD4+ T-cell count and HIV RNA level, the hazard ratio with earlier ART was 0.86 (95% CI, 0.42 to 1.85; P=0.72). The probability of observing 18 AIDS cases or deaths in the earlier-ART group and 19 cases in the later-ART group was 5.6%, 1.9%, and 0.4%, if the true difference in AIDS cases or deaths between the groups was 40%, 50%, and 60%, respectively. In a sensitivity analysis in which all participants lost to follow-up were classified as having died, the incidence was 17.0 cases per 100 person-years (95% CI, 12.3 to 22.8) in the earlier-ART group and 21.7 per 100 person years (95% CI, 16.3 to 28.4) in the later-ART group (incidence-rate ratio, 0.78; 95% CI, 0.51 to 1.19; P=0.23).

INCIDENCE RATES OF AIDS OR DEATH ACCORDING TO CD4+ T-CELL COUNT

A significant interaction between therapy group and CD4+ T-cell count was observed for AIDS or death (P=0.03), indicating heterogeneity across the two CD4+ strata in the effect of time to initiation of ART on the incidence of AIDS or death. The incidence rates of AIDS or death among the 72 patients with CD4+ T-cell counts of less than 50 per cubic millimeter were 8.5 cases per 100 person-years (95% CI, 2.3 to 21.9) in the earlier-ART group as compared with 26.3 per 100 person-years (95% CI, 12.6 to 48.4) in the later-ART group (incidence-rate ratio, 0.32; 95% CI, 0.07 to 1.13; P=0.06) (Table 2

Table 1. Baseline Characteristics of the Patients.*

Variable	Earlier ART (N=214)	Later ART (N=215)	Total (N=429)	P Value
Age — yr				0.75
Mean	34.3±8.0	34.5±8.7	34.4±8.4	
Range	19–63	21–72	19–72	
Male sex — no. (%)	97 (45.3)	112 (52.1)	209 (48.7)	0.18
Educational level — no. (%)†				0.23
Primary school or less	43 (20.2)	49 (22.9)	92 (21.5)	
Some secondary school	97 (45.5)	108 (50.5)	205 (48.0)	
Completed secondary school	73 (34.3)	57 (26.6)	130 (30.4)	
Employed — no. (%)	135 (63.1)	117 (54.4)	252 (58.7)	0.08
History of tuberculosis — no. (%)	80 (37.4)	68 (31.6)	148 (34.5)	0.22
Karnofsky performance score — no. (%)‡				0.84
90 or 100	123 (57.5)	128 (59.5)	251 (58.5)	
70 or 80	86 (40.2)	81 (37.7)	167 (38.9)	
<70	5 (2.3)	6 (2.8)	11 (2.6)	
WHO stage 4 HIV infection — no. (%)§	14 (6.5)	11 (5.1)	25 (5.8)	0.54
Presence of extrapulmonary tuberculosis — no. (%)	10 (4.7)	9 (4.2)	19 (4.4)	0.82
Resistance to tuberculosis drugs — no./total no. (%)				
Isoniazid	13/102 (12.7)	5/101 (5.0)	18/203 (8.9)	0.08
Rifampin	8/102 (7.8)	4/101 (4.0)	12/203 (5.9)	0.37
Ethambutol	1/101 (1.0)	0/100 (0.0)	1/201 (0.5)	1.00
Multidrug resistance	6/102 (5.9)	3/101 (3.0)	9/203 (4.4)	0.50
CD4+ T-cell count — cells/mm^3¶				0.93
Median	154	149	150	
Interquartile range	75–261	77–244	77–254	
Viral load — $\log_{10}$ copies/ml‖				0.53
Median	5.1	5.2	5.2	
Interquartile range	4.5–5.6	4.5–5.6	4.5–5.6	
No. of days of tuberculosis therapy at randomization				0.49
Median	9	9	9	
Interquartile range	7–13	7–14	7–14	

* Plus–minus values are means ±SD.
† Data on educational level were not available for one patient in each group.
‡ The Karnofsky performance score is a measure of the patient's general condition and degree of autonomy on a scale ranging from 0 to 100, with lower numbers indicating poorer function.
§ The remainder of patients had stage 3 infection, according to criteria of the World Health Organization (WHO).
¶ Patients underwent randomization on the basis of the CD4+ T-cell count at screening (criterion for study enrollment, <500 per cubic millimeter). However, for 16 patients, the CD4+ T-cell count at enrollment was 500 per cubic millimeter or higher.
‖ Data on the viral load at baseline were not available for 16 patients in each group.

and Fig. 2). Among the 357 patients with baseline CD4+ T-cell counts of 50 per cubic millimeter or higher, the incidence rates of AIDS or death were 6.6 cases per 100 person-years (95% CI, 3.6 to 11.0) and 4.4 per 100 person-years (95% CI, 2.0 to 8.3) in the earlier-ART and later-ART groups, respectively (incidence-rate ratio, 1.51; 95% CI, 0.61 to 3.95; P=0.34).

IRIS

Among patients with a CD4+ T-cell count of less than 50 per cubic millimeter, the incidence of IRIS was 4.7 times as high in the earlier-ART group as in the later-ART group (P=0.01) (Table 2). Among patients with a CD4+ T-cell count of 50 per cubic millimeter or higher, the incidence of IRIS was 2.2 times as high in the earlier-ART group as in the

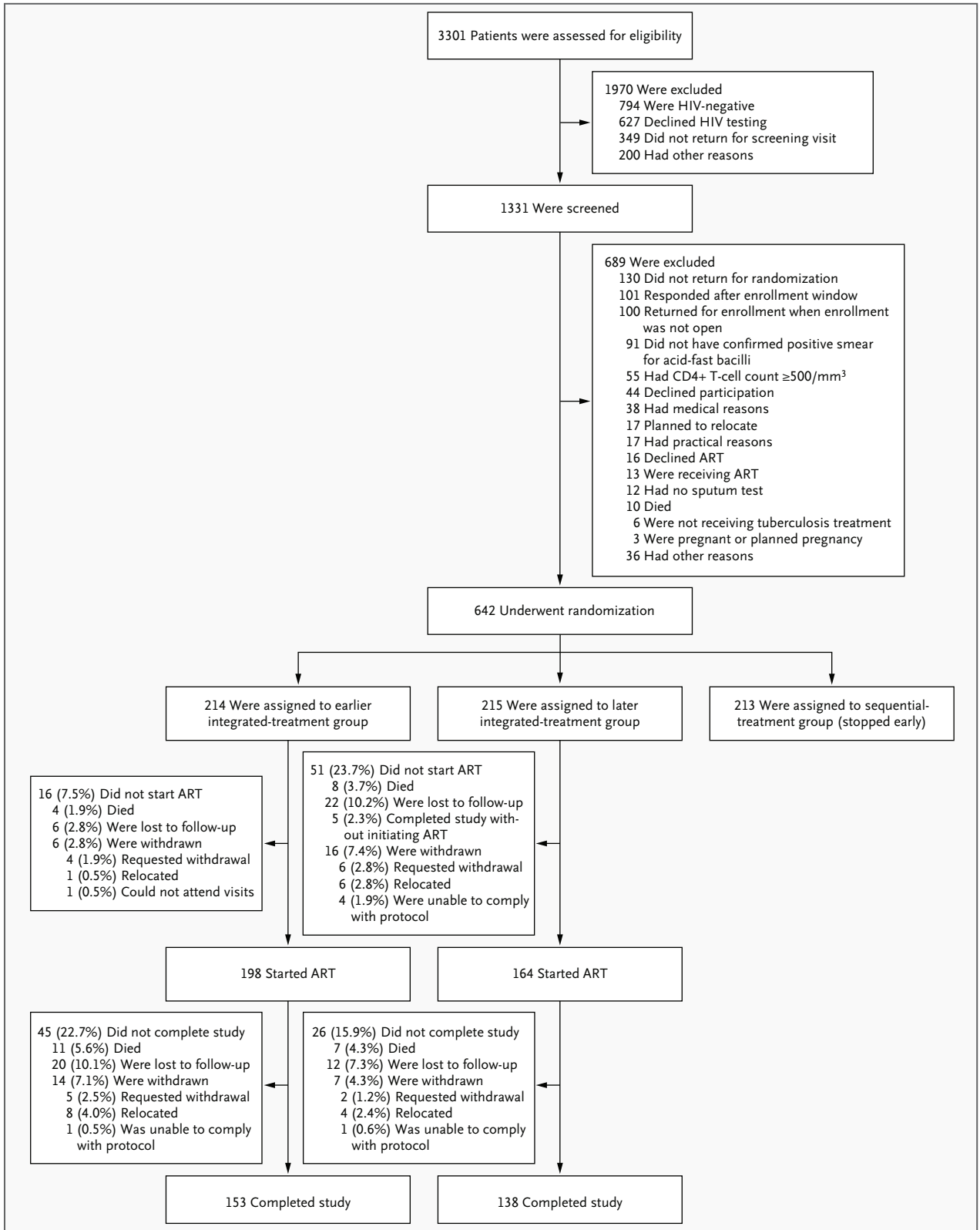

Figure 1. Enrollment and Outcomes.

Loss to follow-up was defined as no visit during the previous 4 months. ART denotes antiretroviral therapy.

later-ART group (P=0.02) (Table 2, and Table 1 in the Supplementary Appendix). No significant interaction was observed that would indicate a lack of heterogeneity across the two CD4+ strata in the effect of time to the initiation of ART on the incidence of IRIS. The median time from the initiation of ART to the development of IRIS was 15.0 days (interquartile range, 7 to 30) in the earlier-ART group and 15.5 days (interquartile range, 14 to 28) in the later-ART group.

ADHERENCE TO THERAPY AND SWITCHING OF DRUGS

Nineteen patients in each of the two study groups were considered to have defaulted tuberculosis therapy (8.9% and 8.8% in the earlier-ART and later-ART groups, respectively), either if they chose to interrupt therapy or if they did not attend the clinic for any further scheduled study visits before treatment completion. According to monthly pill counts, patients in the earlier-ART and later-ART groups took 98.0% and 98.8% of their assigned antiretroviral tablets, respectively, during the trial.

Ten patients in the earlier-ART group and one patient in the later-ART group needed to switch antiretroviral drugs because of adverse events (P=0.006). Among patients with CD4+ T-cell counts of 50 per cubic millimeter or higher, seven patients in the earlier-ART group and one patient in the later-ART group switched antiretroviral drugs (P=0.04).

A total of 15 patients (6 in the earlier-ART group and 9 in the later-ART group) changed their ART regimens because of virologic failure (defined as a viral load >1000 copies per milliliter on two occasions at least 4 weeks apart). The instances of drug switching occurred an average of 9.0 months (95% CI, 5.9 to 12.2) and 11.9 months (95% CI, 9.1 to 14.6) after the initiation of ART in the earlier-ART and later-ART groups, respectively (P=0.18).

OUTCOMES OF TUBERCULOSIS AND HIV TREATMENT

There was no significant difference between the study groups in resistance to tuberculosis drugs at baseline (Table 1). Outcomes of tuberculosis treatment did not differ significantly between the groups (Table 3, and Table 2 in the Supplementary Appendix); this finding did not change after adjustment for the presence or absence of multidrug resistance. At 6 and 12 months after randomization, the proportions of participants with a suppressed HIV RNA level did not differ significantly between

Table 2. Rates of Death, AIDS-Defining Illness or Death, and IRIS, According to Baseline CD4+ T-Cell Count.*

Outcome and CD4+ T-Cell Count	Earlier ART				Later ART				Incidence-Rate Ratio (95% CI)	P Value
	no. of patients	*no. of person-yr*	*no. of events*	*event rate/ 100 person-yr (95% CI)*	*no. of patients*	*no. of person-yr*	*no. of events*	*event rate/ 100 person-yr (95% CI)*		
Death										
All patients	214	261.7	15	5.7 (3.2–9.5)	215	250.9	15	6.0 (3.3–9.9)	0.96 (0.44–2.10)	0.91
CD4+ count <50/mm^3	37	47.5	3	6.3 (1.3–18.5)	35	43.1	7	16.3 (6.5–33.5)	0.39 (0.06–1.70)	0.17
CD4+ count ≥50/mm^3	177	214.2	12	5.6 (2.9–9.8)	180	207.8	8	3.8 (1.7–7.6)	1.46 (0.55–4.10)	0.41
AIDS-defining illness or death										
All patients	214	259.4	18	6.9 (4.1–11.0)	215	244.2	19	7.8 (4.7–12.2)	0.89 (0.44–1.79)	0.73
CD4+ count <50/mm^3	37	46.8	4	8.5 (2.3–21.9)	35	38.0	10	26.3 (12.6–48.4)	0.32 (0.07–1.13)	0.06
CD4+ count ≥50/mm^3	177	212.6	14	6.6 (3.6–11.0)	180	206.2	9	4.4 (2.0–8.3)	1.51 (0.61–3.95)	0.34
IRIS										
All patients	214	213.4	43	20.1 (14.6–27.1)	215	233.6	18	7.7 (4.6–12.2)	2.62 (1.48–4.82)	<0.001
CD4+ count <50/mm^3	37	29.9	14	46.8 (25.6–78.4)	35	40.3	4	9.9 (2.7–25.4)	4.71 (1.48–19.64)	0.01
CD4+ count ≥50/mm^3	177	183.4	29	15.8 (10.6–22.7)	180	193.3	14	7.2 (4.0–12.1)	2.18 (1.12–4.47)	0.02

* Incidence-rate ratios are for the earlier-ART group, as compared with the later-ART group. IRIS denotes immune reconstitution inflammatory syndrome.

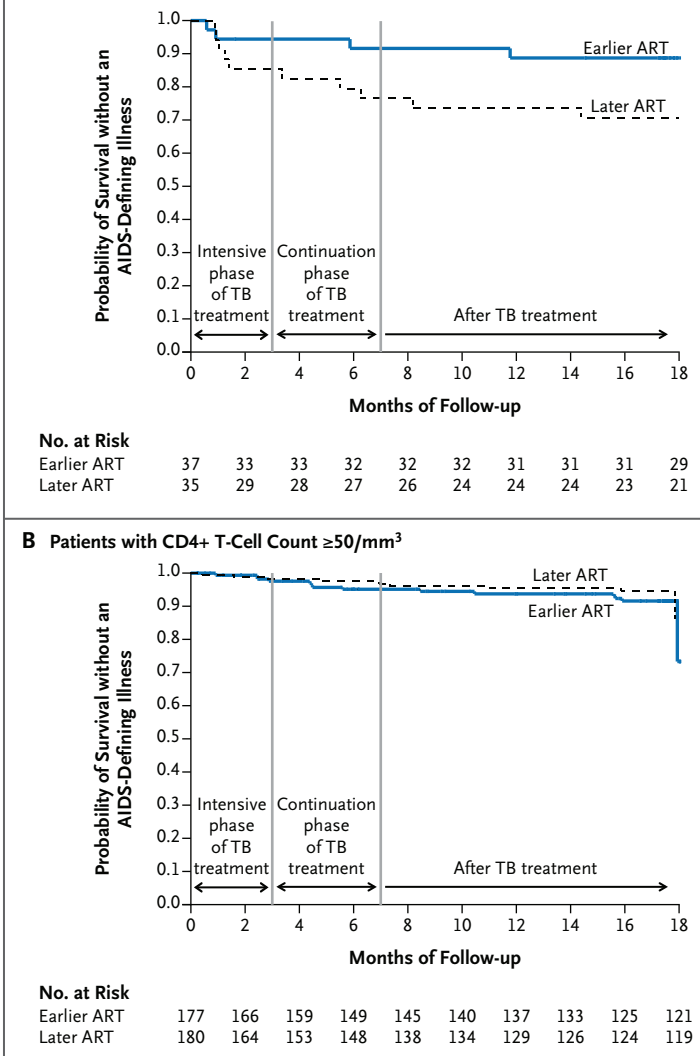

Figure 2. Kaplan–Meier Curves for Survival without an AIDS-Defining Illness.
Panel A shows the data for patients with a CD4+ T-cell count of less than 50 per cubic millimeter, and Panel B shows the data for patients with higher CD4+ T-cell counts. TB denotes tuberculosis.

the earlier-ART and later-ART groups. However, the mean increases from baseline in the CD4+ T-cell count at 12 and 18 months were significantly higher in the earlier-ART group than in the later-ART group (Table 4).

ADVERSE EVENTS

Grade 3 or 4 non-IRIS adverse events occurred in 112 patients in the earlier-ART group and in 107 patients in the later-ART group (42.8 and 42.6 events per 100 person-years, respectively; P=0.98); serious adverse events occurred in 56 and 50 patients in the respective groups. Table 3 in the Supplementary Appendix provides details of the adverse events.

DISCUSSION

Overall, the rates of AIDS or death did not differ significantly between the patients who received early integrated ART and those who received late integrated ART, but the earlier-ART group had higher rates of IRIS and switching of antiretroviral drugs because of adverse events. However, the findings in severely immunocompromised patients differed. In the subgroup of patients with CD4+ T-cell counts of less than 50 per cubic millimeter, earlier ART was associated with a rate of AIDS or death that was about two thirds lower than the rate with later ART; this benefit outweighs the significantly higher rates of IRIS (incidence-rate ratio, 4.7) and of switching of antiretroviral drugs associated with earlier ART. For patients with CD4+ T-cell counts of less than 50 per cubic millimeter, our findings support the 2009 WHO recommendation[8] to start ART as soon as possible after the initiation of tuberculosis treatment.

Our findings suggest a different approach for patients with tuberculosis and HIV who have a CD4+ T-cell count of 50 per cubic millimeter or higher. The initiation of ART during the first 4 weeks of the continuation phase of tuberculosis treatment versus initiation during the first 4 weeks of the intensive phase of tuberculosis treatment was not associated with an increased risk of AIDS or death but was associated with about half the risk of IRIS and a significantly lower risk of the need to switch antiretroviral drugs because of adverse events. Thus, for this subgroup of patients, ART can be deferred until the start of the continuation phase of tuberculosis treatment. However, a longer delay should be avoided, in light of our previous finding that sequential ART (after the completion of tuberculosis treatment) was associated with 56% higher mortality, as compared with its initiation during tuberculosis treatment.[6]

Some limitations of our study need to be considered. First, the observed 68% lower rate of AIDS or death among severely immunocompromised patients as compared with the rate among other patients (incidence-rate ratio, 0.32), although substantial, was not significant (P=0.06). However, it is unlikely that this finding was due to chance, because a survival benefit in severely immunocompromised patients was also observed in the Cam-

Table 3. Clinical Outcomes of Tuberculosis Treatment.

Outcome	Baseline CD4+ T-Cell Count <50/mm³		Baseline CD4+ T-Cell Count ≥50/mm³	
	Earlier ART (N=37)	Later ART (N=35)	Earlier ART (N=177)	Later ART (N=180)
	number of patients (percent)			
Tuberculosis cured*	23 (62)	24 (69)	108 (61)	114 (63)
Tuberculosis treatment successfully completed†	8 (22)	4 (11)	32 (18)	34 (19)
Treatment successful‡	31 (84)	28 (80)	140 (79)	148 (82)
Patient died before tuberculosis treatment completed	3 (8)	4 (11)	11 (6)	7 (4)
Treatment interruption	0	1 (3)	5 (3)	3 (2)
Treatment failure with first-line regimen§	1 (3)	0	5 (3)	2 (1)
Patient lost to follow-up before tuberculosis treatment completed	1 (3)	1 (3)	12 (7)	15 (8)
Patient transferred to other clinic, tuberculosis treatment outcome not known	1 (3)	1 (3)	4 (2)	5 (3)

* Tuberculosis cure was defined in accordance with the *South African National Tuberculosis Control Programme Practical Guidelines 2004*, which states, "Patient who is smear-negative at, or one month prior to, the completion of treatment and also on at least one previous occasion." Most study patients were unable to produce sputum after the first few months of tuberculosis treatment, making demonstration of a cure difficult.
† Successful completion of treatment was defined as the use of more than 85% of the prescribed medication.
‡ Treatment success was defined as tuberculosis cure and successful completion of tuberculosis treatment.
§ Treatment failure was defined as a positive smear or culture for *Mycobacterium tuberculosis* that was obtained at least 5 months after the initiation of tuberculosis therapy.

bodian Early versus Late Introduction of Antiretrovirals study (CAMELIA; ClinicalTrials.gov number, NCT01300481). In the Cambodian study, among patients coinfected with tuberculosis and HIV who had a median CD4+ T-cell count of 25 per cubic millimeter, those who started ART 2 weeks after the initiation of tuberculosis treatment had 38% lower mortality than those who waited 8 weeks to start ART (P=0.006).[9] Among patients with CD4+ T-cell counts below 50 per cubic millimeter in the AIDS Clinical Trials Group Study A5221 (NCT00108862), 15.5% of patients in the earlier-ART group versus 26.6% in the later-ART group had an AIDS-defining illness or died (95% CI, 1.5 to 20.5; P=0.02).[10]

Second, the lack of a survival benefit in patients with CD4+ T-cell counts of 50 per cubic millimeter or higher may be due to the sample size (357 patients) and the small number of deaths observed. There would be only a 9.2% probability of observing these rates of death if the true difference in mortality between the earlier-ART and later-ART groups was 34% or greater. Furthermore, the limited observational data available show similar trends. In a pilot study of the initiation of ART involving 70 patients with a median CD4+ T-cell count of 103 per cubic millimeter, there were 2 deaths in the early-therapy group (within 2 weeks after the start of tuberculosis treatment) versus 1 death in the delayed-therapy group (8 weeks after the start of tuberculosis treatment) (P=0.601).[11]

Third, inaccuracies in the diagnosis of IRIS, and therefore in the reported incidence of the syndrome, may have affected the study outcome. The incidence rate of 14.2% observed in this study is consistent with findings from other South African studies. In one study of patients coinfected with tuberculosis and HIV, the incidence of IRIS was 12% overall, yet 32% of patients who started ART within 2 months after receiving a diagnosis of tuberculosis had an IRIS event.[12] The risk of IRIS remained elevated if ART was started within 3 months after the initiation of tuberculosis treatment, but it was highest during the first month of tuberculosis treatment. A retrospective analysis of 627 patients from India showed that 7.6% of patients with tuberculosis (18 of 237) had paradoxical tuberculosis-associated IRIS, and 3.1% of patients without tuberculosis (12 of 390) had IRIS associated with ART.[13] A low CD4+ T-cell count at baseline and early initiation of ART

Table 4. Clinical Outcomes of ART.

Outcome and Baseline CD4+ T-Cell Count	Earlier ART		Later ART		P Value
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	
Viral load <400 copies/ml					
At 6 mo after initiation of ART					
Overall	161/179	89.9 (84.3–93.8)	166/179	92.7 (87.6–95.9)	0.45
CD4+ count <50/mm³	30/34	88.2 (71.6–96.2)	32/35	91.4 (75.8–97.8)	0.71
CD4+ count ≥50/mm³	131/145	90.3 (84.0–94.4)	134/144	93.1 (87.3–96.4)	0.52
At 12 mo after randomization					
Overall	147/159	92.5 (86.9–95.9)	130/147	88.4 (81.9–92.9)	0.25
CD4+ count <50/mm³	30/32	93.8 (77.8–98.9)	23/27	85.2 (65.4–95.1)	0.40
CD4+ count ≥50/mm³	117/127	92.1 (85.6–96.0)	107/120	89.2 (81.9–93.9)	0.51
At 18 mo after randomization					
Overall	144/153	94.1 (88.8–97.1)	135/143	94.4 (88.9–97.4)	1.00
CD4+ count <50/mm³	28/30	93.3 (76.5–98.8)	25/26	96.2 (78.4–99.8)	1.00
CD4+ count ≥50/mm³	116/123	94.3 (88.2–97.5)	110/117	94.0 (87.6–97.4)	1.00
	no. of patients	*mean increase (95% CI)*	*no. of patients*	*mean increase (95% CI)*	
Mean increase in CD4+ count					
At 6 mo after initiation of ART					
Overall	178	132 (113–152)	179	132 (111–152)	0.95
CD4+ count <50/mm³	34	124 (94–154)	35	104 (83–124)	0.25
CD4+ count ≥50/mm³	144	134 (111–157)	144	138 (113–163)	0.82
At 12 mo after randomization					
Overall	159	183 (162–204)	147	125 (105–145)	0.009
CD4+ count <50/mm³	32	170 (127–213)	27	111 (81–141)	0.03
CD4+ count ≥50/mm³	127	186 (163–210)	120	128 (104–152)	0.001
At 18 mo after randomization					
Overall	152	217 (192–243)	142	172 (150–194)	0.009
CD4+ count <50/mm³	30	207 (166–248)	26	173 (134–212)	0.22
CD4+ count ≥50/mm³	122	220 (189–251)	116	172 (146–198)	0.02

were significantly associated with paradoxical tuberculosis-associated IRIS.

The rates of adverse events in the earlier-ART and later-ART groups were not substantially different. Published data on additive treatment-related toxic effects in patients receiving treatment for both tuberculosis and HIV infection are limited. A retrospective study in India showed that concomitant use of ART and tuberculosis treatment was a predictor of adverse events (odds ratio, 1.88).[14] Furthermore, a study from Thailand showed that 44.6% of patients receiving treatment for tuberculosis and HIV had adverse events due to antituberculosis drugs or ART.[15] Of these patients, 66% had adverse events within the first 2 months after the start of tuberculosis treatment, and 76.8% had to stop or change either antituberculosis or antiretroviral drugs. In contrast, a retrospective study from South Africa showed that the occurrence of serious adverse events was unrelated to the use of antiretroviral drugs in patients with tuberculosis.[16]

In our study, there were no significant differences between the earlier-ART and later-ART groups in the outcomes of tuberculosis treatment

or in the proportion of participants with a suppressed viral load. However, significant increases in the CD4+ T-cell count at 12 and 18 months were observed in the earlier-ART group, probably as a result of the longer duration of ART as compared with the duration in the later-ART group. This finding may have implications for longer-term survival, for which long-term follow-up would be needed.

These results of the SAPIT study further support the integration of treatment for tuberculosis and HIV infection. The current WHO recommendation to initiate ART as soon as possible after the start of tuberculosis treatment, regardless of the CD4+ T-cell count, may need to be revisited in view of the findings of this study. We found that early initiation of ART in patients with CD4+ T-cell counts of less than 50 per cubic millimeter increased AIDS-free survival, whereas deferral of the initiation of ART to the first 4 weeks of the continuation phase of tuberculosis therapy in those with higher CD4+ T-cell counts reduced the risks of IRIS and other adverse events related to ART without increasing the risk of AIDS or death.

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