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.)
INTEGRATION OF ART WITH TB 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. 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 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. 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).
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 later-ART group.
Table 1. Enrollment and Outcomes.
Loss to follow-up was defined as no visit during the previous 4 months. ART denotes antiretroviral therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Did not start ART</th>
<th>Died</th>
<th>Lost to follow-up</th>
<th>Requested withdrawal</th>
<th>Relocated</th>
<th>Unable to comply with protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earlier integrated-treatment</td>
<td>16 (7.5%)</td>
<td>4 (1.9%)</td>
<td>6 (2.8%)</td>
<td>4 (1.9%)</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Sequential-treatment</td>
<td>51 (23.7%)</td>
<td>8 (3.7%)</td>
<td>22 (10.2%)</td>
<td>5 (2.3%)</td>
<td>16 (7.4%)</td>
<td>6 (2.8%)</td>
</tr>
<tr>
<td>Completed study</td>
<td>153</td>
<td>8 (4.3%)</td>
<td>12 (7.3%)</td>
<td>7 (4.3%)</td>
<td>2 (1.2%)</td>
<td>4 (2.4%)</td>
</tr>
</tbody>
</table>
Integrating Art With TB Treatment

**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 the earlier-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.

| 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      | P Value        |
|                                        | no. of patients | no. of patients | no. of patients | no. of patients | incidence-rate ratio (95% CI) |
| Death                                   |                |                |                |                |                              |
| All patients                            | 214            | 215            | 0.91           |
| CD4+ count <50/mm³                      | 15             | 15             | 1.01 (0.43–2.4) |
| CD4+ count ≥50/mm³                      | 200.9          | 200.9          | 0.99 (0.44–2.10) |
| AIDS-defining illness or death          |                |                |                |                |                              |
| All patients                            | 214            | 215            | 0.73           |
| CD4+ count <50/mm³                      | 35             | 35             | 0.69 (0.44–1.0) |
| CD4+ count ≥50/mm³                      | 180            | 180            | 0.89 (0.44–1.79) |
| IRIS                                    |                |                |                |                |                              |
| All patients                            | 214            | 215            | 0.01           |

* 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.

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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).

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).

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). 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. 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.

A low CD4+ T-cell count at baseline and early initiation of ART

<table>
<thead>
<tr>
<th>Table 3. Clinical Outcomes of Tuberculosis Treatment.</th>
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<tbody>
<tr>
<td>Outcome</td>
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<tr>
<td></td>
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<tr>
<td>Tuberculosis cured*</td>
</tr>
<tr>
<td>Tuberculosis treatment successfully completed†</td>
</tr>
<tr>
<td>Treatment successful‡</td>
</tr>
<tr>
<td>Patient died before tuberculosis treatment completed</td>
</tr>
<tr>
<td>Treatment interruption</td>
</tr>
<tr>
<td>Treatment failure with first-line regimen§</td>
</tr>
<tr>
<td>Patient lost to follow-up before tuberculosis treatment completed</td>
</tr>
<tr>
<td>Patient transferred to other clinic, tuberculosis treatment outcome not known</td>
</tr>
</tbody>
</table>

* 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.
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).

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. 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.

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.

REFERENCES