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Integration of Antiretroviral Therapy with Tuberculosis Treatment

Salim S. Abdool Karim, MBChB, PhD[1,2,3], **Kogieleum Naidoo, MBChB**[1], **Anneke Grobler, MSc**[1], **Nesri Padayatchi, MBChB**[1,2], **Cheryl Baxter, MSc**[1], **Andrew L. Gray, MSc(Pharm)**[2], **Tanuja Gengiah, MClin Pharm, MS (Epi)**[1], **Santhanalakshmi Gengiah, MA(Res Psych)**[1], **Anushka Naidoo, MMedSci(Pharm)**[1], **Niraksha Jithoo, MBChB**[1], **Gonasagrie Nair, MBChB, MPH**[1], **Wafaa M. El-Sadr, MD, MPH**[3,4], **Gerald Friedland, MD**[5], and **Quarraisha Abdool Karim, PhD**[1,2,3]

[1]Centre for the AIDS Programme of Research in South Africa (CAPRISA), South Africa

[2]University of KwaZulu-Natal, Durban, South Africa

[3]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA

[4]ICAP, Mailman School of Public Health, Columbia University, New York, USA

[5]Yale University, New Haven, Connecticut, USA

Abstract

Background—We previously reported that integrating antiretroviral therapy (ART) with tuberculosis treatment reduces mortality. However, optimal time to initiate ART during tuberculosis treatment remains contentious.

Methods—To address this, we conducted a 3-arm, open-label randomized controlled trial in South Africa in acid-fast bacilli smear positive patients (n=642) with HIV and CD4+ counts <500 cells/mm^3. Findings on the early therapy group (ART initiated within 4 weeks of tuberculosis treatment initiation, n=214) and late therapy group (ART initiated within the first 4 weeks of the continuation phase of tuberculosis treatment, n=215) are presented here.

Results—Median CD4+ count and viral load at baseline was 150 cells/mm^3 and 161000 copies/ml, being similar in both groups. Incidence rate of AIDS or death was 6.9 (18/259.4) and 7.8 (19/244.2) per 100 person-years in the early and late therapy groups respectively (Incidence Rate Ratio (IRR)=0.89; 95%Confidence Interval (95%CI): 0.44,1.79; P=0.73). However, in patients with CD4+ counts <50 cells/mm^3, the incidence rates of AIDS or death were 8.5 (early) and 26.3 (late) per 100 person-years (IRR=0.32; 95%CI: 0.07,1.13; P=0.06). Immune reconstitution inflammatory syndrome (IRIS) incidence rates were 20.2 (early) and 7.7 (late) per 100 person-years (IRR=2.62; 95%CI: 1.48,4.82; P<0.001). Adverse events requiring antiretroviral drug switches occurred in 10 (early) and 1 (late) patients (P=0.006).

Conclusions—The benefits of AIDS-free survival balanced against the risks of IRIS and ART-related adverse events, support early ART initiation in patients with CD4+ counts <50 cells/mm^3

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Dr. S. Abdool Karim reports being listed as a coinventor on two patents (2000/3437 and PCT/IB02/04550) that are part of the development of clade C HIV vaccines; and Mr. Gray, receiving lecture fees from AstraZeneca, Aspen Pharmacare, and Fresenius Kabi. No other potential conflict of interest relevant to this article was reported.

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and deferred ART initiation to the continuation phase of tuberculosis treatment when CD4+ counts are higher.

We previously reported that integrating antiretroviral therapy (ART) with tuberculosis treatment reduces mortality[1]. In HIV-tuberculosis co-infected patients, antiretroviral therapy may be initiated at the same time or soon after tuberculosis treatment initiation. However, antiretrovirals are often deferred until completion of the intensive phase of tuberculosis treatment because of concerns related to immune reconstitution inflammatory syndrome (IRIS)[2–3], high pill burden and overlapping side effects[4], when three antiretrovirals are added to the standard four anti-tuberculosis drugs. This may result in interruptions or discontinuations in AIDS or tuberculosis treatment, which can lead to drug resistance and potentially limit future therapeutic options [5–6], but must be weighed against the risk of increased mortality early in the treatment of tuberculosis

The SAPiT (**S**tarting **A**ntiretroviral therapy at three **P**oints **i**n **T**uberculosis) trial[6] was designed to determine the optimal time for initiation of ART in HIV-tuberculosis co-infected patients. Here, we report on the initiation of ART at two points during tuberculosis treatment.

METHODS

This was a prospective, open-label, randomized trial in South Africa. A total of 642 ambulatory patients with pulmonary tuberculosis and HIV co-infection, aged 18 years or older, were enrolled after obtaining written informed consent.

Pulmonary tuberculosis was confirmed by acid fast bacilli smear positivity. HIV-infection was confirmed by two rapid HIV tests. All patients had a screening CD4+ count < 500 cells/mm^3 and were initiated on a standard tuberculosis treatment regimen[7]. All first episode tuberculosis patients were treated a fixed drug combination of rifampicin, isoniazid, ethambutol and pyrazinamide dosed according to pre-treatment weight for 2 months (intensive phase) with subsequent fixed-drug combination of isoniazid and rifampicin for 4 months (continuation phase) for all first episodes of tuberculosis. Patients with re-treatment tuberculosis received a 60 day intensive phase which includes streptomycin, followed by a 100 day continuation phase.

Details of the study methods have been previously reported [1]. The once daily antiretroviral therapy regimen contained enteric-coated didanosine (250mg if weight <60kg and 400mg if weight ≥60kg), lamivudine (300mg) and efavirenz (600mg). Antiretroviral therapy adherence was assessed monthly by pill counts. Notwithstanding their study group assignment, patients could be initiated on antiretroviral therapy at any time at the discretion of the study clinicians or their personal physicians.

The outcome of the sequential therapy group has been previously reported[1]. This analysis comprises complete follow-up data on the 214 patients in the early integrated-therapy group (antiretroviral therapy to be initiated within 4 weeks of starting tuberculosis treatment) and the 215 patients in the late integrated-therapy group (antiretroviral therapy to be initiated within 4 weeks of completing the intensive phase of tuberculosis treatment). The details of the study methods and data on 18 months follow-up of all three study groups are provided in the supplementary appendix (Supplementary Tables 1–3).

All analyses were by intention-to-treat. The trial's primary outcome, AIDS or death rate, was analyzed using 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 post randomization, whichever occurred first. Poisson approximations

were used to calculate confidence intervals for the incidence rate ratios. 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 for the analysis of continuous data. Interactions between therapy group and CD4+ count were evaluated by fitting a proportional hazards model with therapy group, CD4+ count and their interaction.

The trial (NCT00398996) was approved by the University of KwaZulu-Natal's Biomedical Research Ethics Committee (E 107/05) and the Medicines Control Council (MCC ref: 20060157). Study data were reviewed periodically by a Safety Monitoring Committee.

Results

At enrolment (Figure 1), the 214 patients in the early integrated-therapy group and the 215 patients in the late integrated-therapy group had similar demographic and clinical characteristics (Table 1). Median CD4+ count was 150 cells/mm^3 and viral load was 161000 copies/ml at baseline; similar between both groups. Median duration of follow-up in the trial was 17.7 months (interquartile range (IQR), 14.0 to 17.8). At study completion, the retention rates were 76.9% and 71.5% in the early and late integrated-therapy groups respectively (Information on retention and causes of death is provided in the online material).

Initiation of antiretroviral therapy

Among patients who completed tuberculosis therapy, the median treatment duration was 210 days (207 participants) and 203 days (210 participants) in the early and late integrated-therapy groups respectively. A total of 92.5% (198/214) of the patients in the early integrated-therapy group and 76.3% (164/215) in the late integrated-therapy group started antiretroviral therapy during the study (P<0.001). The longer period from randomization to antiretroviral therapy initiation resulted in more patients being lost to follow-up, withdrawing or dying prior to antiretroviral therapy initiation in the late integrated therapy group (Figure 1). However, there are no significant differences in the overall rates of lost-to-follow-up (12.1% vs 15.8%, P=0.33) and withdrawals (9.3% vs 10.7%, P=0.75) between the early and late integrated-therapy groups.

The 198 patients in the early integrated-therapy group, who started antiretroviral therapy, did so at a median of 21 days (IQR 15 to 29) after tuberculosis therapy initiation. Reasons for 33 of these patients initiating antiretroviral therapy after the four-week window were; missed their antiretroviral therapy initiation visit (n=9), abnormal liver function (n=8), other laboratory abnormalities (n=2), refused antiretroviral therapy initiation (n=4), or clinical conditions precluding antiretroviral therapy initiation (n=10).

The 164 patients in the late integrated-therapy group, who started antiretroviral therapy, did so at a median of 97 days (IQR: 77 to 126.5) after the initiation of tuberculosis therapy. One patient started antiretroviral therapy during the intensive phase of tuberculosis treatment. Reasons for 47 of these patients starting antiretroviral therapy more than four weeks after completion of the intensive phase of tuberculosis treatment were: missed their antiretroviral therapy initiation visit (n=29), abnormal liver function (n=1), refused antiretroviral therapy initiation (n=6), or clinical conditions precluding antiretroviral therapy initiation (n=11).

Incidence rates of AIDS or death

Incidence rates of AIDS or death were 6.9 (18/259.4) and 7.8 (19/244.2) per 100 person-years in the early and late integrated-therapy groups respectively (Incidence Rate Ratio (IRR), 0.89; 95%Confidence Interval (95%CI), 0.44 to 1.79; P=0.73). After adjustment for baseline WHO disease stage (stage 4 vs. stage 3), age, sex, history of tuberculosis,

extrapulmonary tuberculosis, and baseline CD4+ cell count and HIV RNA level, the hazard ratio was 0.86 (95% CI, 0.42 to 1.85). The probability of observing 18 of AIDS or death cases in the early ART group and 19 cases in the late ART group was 5.6%, 1.9%, and 0.4% if the true difference in AIDS or death between the arms was 40%, 50% and 60% respectively. In a sensitivity analysis, where all participants lost to follow-up were regarded as having died, the incidence was 17.0 (95% CI 12.3 to 22.8) and 21.7 per 100 person years (95% CI 16.3 to 28.4) in the early and late integrated arms respectively, (IRR: 0.78, 95% CI: 0.51 to 1.19, P=0.227).

Incidence rates of AIDS or death by CD4+ count

A statistically significant (P = 0.027) interaction between therapy group and CD4+ count for AIDS or death, indicating heterogeneity across the two CD4 strata in the effect of time to ART initiation on AIDS or death. The incidence rates of AIDS or death in the subset of patients with CD4+ counts <50 cells/mm^3 (n=72) were 8.5 per 100 person-years (95%CI, 2.3 to 21.9) in the early integrated-therapy group compared to 26.3 per 100 person-years (95%CI, 12.6 to 48.4) in the late integrated-therapy group (IRR 0.32, 95% CI, 0.07 to 1.13, P=0.06) (Figure 2). In patients enrolled with CD4+ counts ≥50 cells/mm^3 (n=357), the incidence rates of AIDS or death were 6.6 (95%CI, 3.6 to 11.0) and 4.4 (95%CI, 2.0 to 8.3) per 100 person-years in the early and late integrated-therapy groups respectively (IRR, 1.51, 95% CI 0.61 to 3.95, P=0.34) (Table 2).

IRIS

In the early integrated-therapy group, IRIS occurred 4.7 times (P=0.01) more frequently in patients with CD4+ count below 50 cells/mm^3 and 2.2 times (P=0.02) more frequently in patients with CD4+ counts ≥50 cells/mm^3 (Table 2). No statistically significant interaction indicating a lack of heterogeneity across the two CD4 strata in the effect of time to ART initiation on IRIS. The median time from antiretroviral therapy initiation to development of IRIS was 15.0 (IQR, 7 – 30) days in the early integrated-therapy group and 15.5 (IQR, 14 – 28) days in the late integrated-therapy group. Steroid treatment was required by 7 (9.1%) patients with IRIS; 5 of them had CD4+ counts below 50 cells/mm^3.

Adherence and drug switches

Nineteen patients in each of the two study groups are known to have defaulted tuberculosis therapy (8.9% and 8.8% in the early and late integrated-therapy groups respectively), either by choosing to interrupt therapy or by not attending the clinic for any further scheduled study visits before treatment completion.

Based on monthly pill counts, patients in the early integrated-therapy group and the late integrated-therapy group took 98.0% and 98.8% of their assigned antiretroviral tablets, respectively, during the trial.

Antiretroviral drug switches due to toxicity were required for 10 patients in the early integrated-therapy group and for one patient in the late integrated-therapy group (P=0.006). In patients with CD4+ counts ≥ 50 cells/mm^3, antiretroviral therapy switches occurred in seven patients in the early therapy group and in one patient in the late therapy group (P=0.04).

A total of 15 patients changed their antiretroviral regimens due to virological failure; 6 in the early integrated-therapy group and 9 in the late integrated therapy-group. The antiretroviral drug switches occurred on average 9.0 (95%CI: 5.9 to 12.2) and 11.9 (9.1 to 14.6) months after antiretroviral therapy initiation in the early and late integrated-therapy groups respectively (P=0.18).

Tuberculosis and HIV treatment outcomes

There is no statistically significant difference in tuberculosis drug resistance (Table 1) at baseline between the study groups. Tuberculosis treatment outcomes did not differ between the groups (Table 3); this did not change after adjustment for presence of multi-drug resistance. At 6 and 12 months after randomization, the proportion of participants with a suppressed HIV RNA level did not differ between the integrated-therapy groups. However, the mean CD4+ count increase from baseline to 12 and 18 months post randomization was significantly higher in the early integrated-therapy group compared to the late integrated-therapy group (Table 3).

Adverse events

There were 112 and 107 patients with grade 3/4 non-IRIS adverse events in the early (42.8 per 100 person-years) and late (42.6 per 100 person-years) integrated-therapy groups, respectively (P=0.98). There were 56 and 50 patients with serious adverse events in the early and late integrated-treatment groups respectively.

Discussion

Overall, the AIDS or death rates did not differ in the early and late integrated-therapy groups, but the early group had higher rates of IRIS and antiretroviral drug switches due to adverse events. However, the findings in severely immunocompromised patients differed. In the subset of patients with CD4+ counts <50 cells/mm^3, early integrated antiretroviral therapy was associated with about two-thirds lower risk of AIDS or death, outweighing the 5-fold higher rate of IRIS and the significantly higher rates of antiretroviral drug switching due to adverse events. For patients with CD4+ counts below 50 cells/mm^3, our findings support the 2009 WHO recommendation[8] to start antiretroviral therapy as soon as possible after starting TB treatment.

This study's findings suggest a different approach for patients with tuberculosis and HIV who have CD4+ cell count ≥50 cells/mm^3. Initiation of antiretroviral therapy during the continuation phase instead of the first 4 weeks after initiation of tuberculosis treatment did not demonstrate an increased risk of AIDS or death but was associated about half the risk of IRIS and significantly lower risk of antiretroviral drug switches due to adverse events. Thus, for this subset of patients, antiretroviral therapy can be deferred until the start of the continuation phase of tuberculosis treatment. It is important to note that deferment of antiretroviral therapy initiation to the continuation phase of tuberculosis treatment should avoid lengthy delays in light of our previous finding that the sequential antiretroviral therapy to after completion of tuberculosis treatment was associated with 56% higher mortality when compared to its initiation during tuberculosis treatment[1].

Some limitations in our study need to be considered. First, the observed 68% (IRR=0.32) lower rate of AIDS or death in severely immunocompromised patients, while substantial, was not statistically significant (P=0.06). However, it is unlikely that this finding was due to chance as a survival benefit in severely immunocompromised patients was also observed in the Cambodian Early versus Late Introduction of Antiretrovirals(CAMELIA) study, which reported a 38% lower mortality (P=0.006) among tuberculosis-HIV co-infected patients with a median CD4+ count of 25 cells/mm^3 who initiated antiretroviral therapy within two weeks of anti-tuberculosis therapy compared to patients who waited eight weeks to initiate antiretroviral therapy[9].

Second, the lack of a survival benefit in patients with CD4+ counts ≥50 cells/mm^3 may be due to the sample size (n=357) and the limited number of deaths observed. There is only a 9.2%, probability of observing these mortality rates if the true difference in mortality

between the early and late integrated-therapy groups was 34% or greater. Further, the limited observational data available, show similar trends. A 70 patient pilot study of antiretroviral therapy initiation among patients (median CD4+ count = 103 cells/mm^3) observed two deaths in the early group (2 week) versus one death in the delayed group (8 weeks) (p=0.601)[10].

Third, inaccuracies in the IRIS incidence and diagnosis could impact the study outcome. The IRIS incidence rate of 14.2% observed in this study is consistent with findings from other South African studies. In one study[11] of tuberculosis and HIV co-infected patients, the IRIS incidence was 12% overall. In the latter study, 32% of patients who initiated antiretroviral therapy within 2 months of tuberculosis diagnosis experienced an IRIS event, with a continued high risk if initiated within 3 months but highest if antiretroviral therapy was initiated within 1 month of tuberculosis treatment[11]. A retrospective analysis of 627 patients from India[12] showed that 7.6% (18/237) of tuberculosis patients had paradoxical tuberculosis-associated IRIS, and 3.1% (12/390) of the patients without tuberculosis developed antiretroviral therapy-associated IRIS. Low CD4+ cell count at baseline and early initiation of antiretroviral therapy were significantly associated with paradoxical tuberculosis-associated IRIS[12].

The adverse events rates in the early and late therapy groups were not substantially different. Published data on additive toxicities in tuberculosis-HIV co-treated patients are limited. A retrospective study in India found concomitant antiretroviral and tuberculosis therapy to be a predictor of adverse events (OR = 1.88)[13]. Further a study from Thailand demonstrated that 44.6% of co-treated patients had adverse drug effects due either to anti-tuberculosis drugs or antiretroviral therapy. Of these, 66% occurred within the first 2 months of tuberculosis treatment, and 76.8% had to stop or change either anti-tuberculosis treatment or antiretroviral therapy[15]. In contrast, a retrospective study from South Africa found that the occurrence of serious adverse events was unrelated to use of antiretroviral drugs in tuberculosis patients[14].

There were no observed differences in tuberculosis treatment outcomes or proportion of participants with suppressed viral load in the early and late integrated-therapy groups. However, a significant difference in the increase in CD4+ count at 12 and 18 months was observed in the early integrated-therapy group, likely due to longer duration on antiretroviral therapy. This may have longer-term survival implications for which long-term follow-up would be needed.

These findings of the SAPiT study further support the integration of tuberculosis and HIV therapy. The current WHO recommendation to initiate antiretroviral therapy as soon as possible after tuberculosis treatment initiation, regardless of CD4+ count, may need to be revisited in view of the findings of this study. Weighing the risks of IRIS morbidity and antiretroviral therapy tolerability with the benefits of AIDS-free survival, we recommend early antiretroviral therapy initiation in patients with CD4+ counts <50 cells/mm^3 and deferred antiretroviral therapy initiation to the first four weeks of the continuation phase of tuberculosis therapy in those with higher CD4+ counts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The study was designed by SSAK, WES, GF, AGray, and QAK. Data was gathered by, KN, NP, NJ, GN, SG, TG, and AN. Data was analysed by AG. SSAK, KN, NP, and AG vouch for data and analysis. KN, SSAK, CB and AG wrote the paper and SSAK decided to publish the paper. We thank the patients for their participation in this study; Prof. Willem Sturm of the Nelson R. Mandela School of Medicine for confirmatory tuberculosis testing; the eThekwini metro and Prince Cyril Zulu Communicable Disease Clinic Management and staff for support of the study; Drs. Gray Handley, Ed Tramont, Rod Hoff, Sandi Lehrman, and Richard Hafner of the Division of AIDS at the National Institutes of Health for study support; Drs. Gavin Churchyard, Douglas Taylor, and Mark Weaver for serving on the data and safety monitoring committee; members of the Community Advisory Board for their advice in the conduct of the SAPIT trial; Ms. Nomapando Barnabas of the CAPRISA Community Programme for overseeing community involvement in the trial; Ms. Natasha Samsunder and Mr. Keith Coetzee for laboratory analysis; Ms. Nonhlanhla Yende for statistical support; Ms. Irene van Middelkoop for data management; and all the other members of the SAPIT study team for their commitment to high quality study conduct

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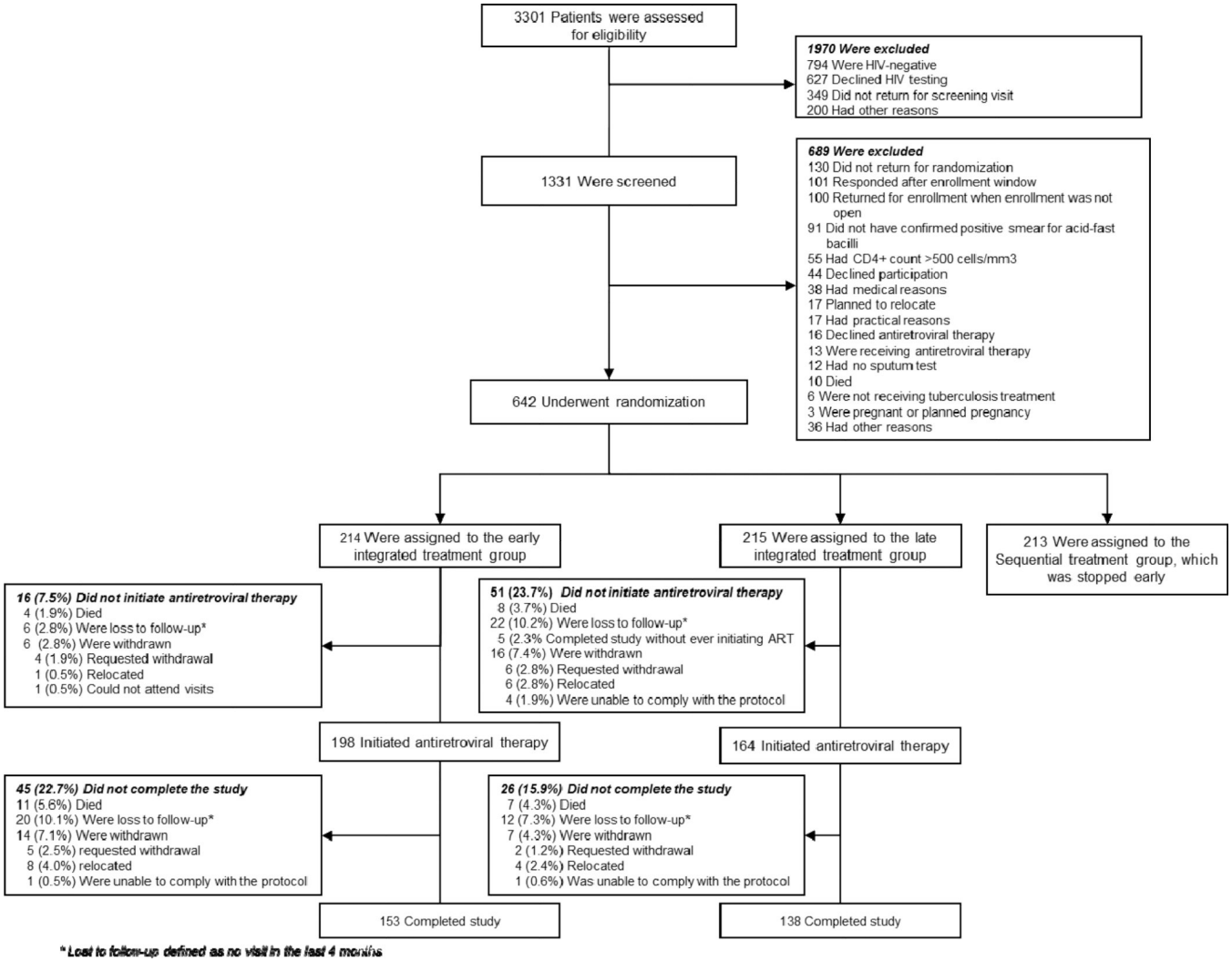
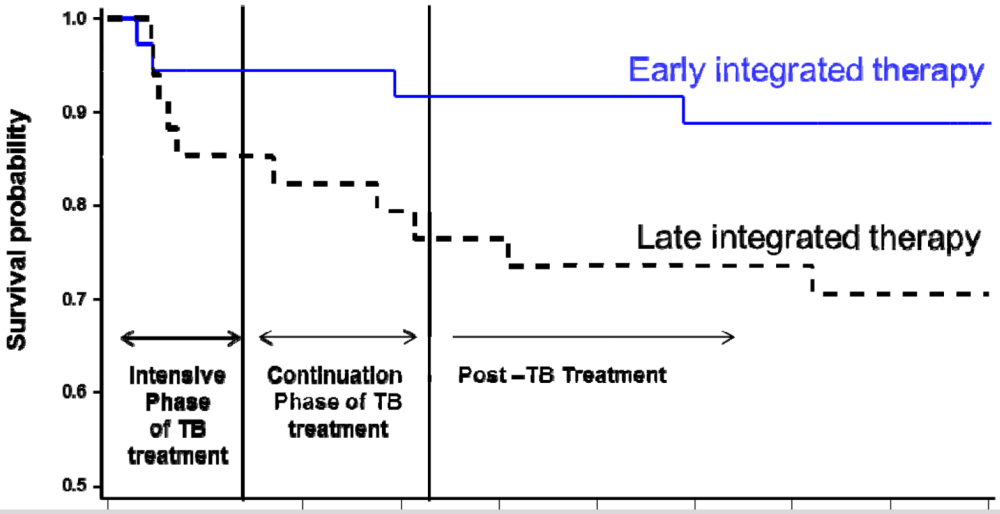


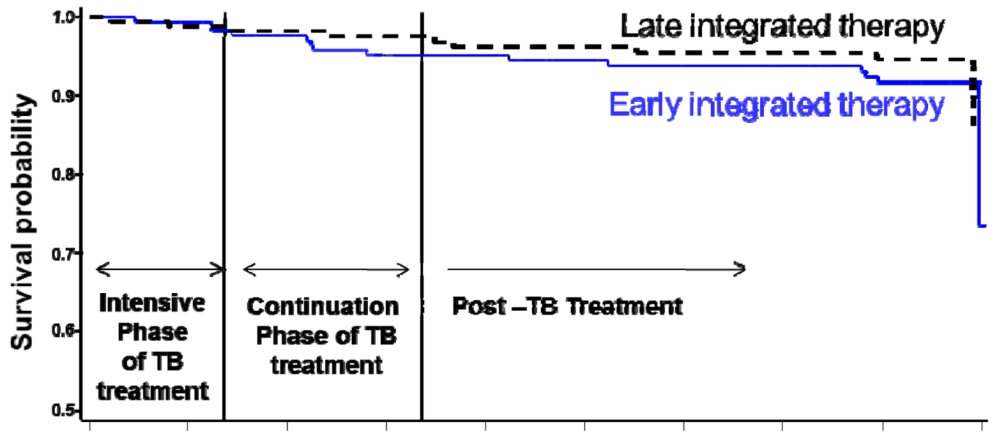
Figure 1.
Enrollment and Outcomes.

a) Patients with CD4 <50 cells/mm^3



Months of follow-up	0	2	4	6	8	10	12	14	16	18
# at risk (early-integrated)	37	33	33	32	32	32	31	31	31	29
# at risk (late integrated)	35	29	28	27	26	24	24	24	23	21

b)Patients with CD4 ≥ 50 cells/mm^3



Months of follow-up	0	2	4	6	8	10	12	14	16	18
# at risk (early integrated)	177	166	159	149	145	140	137	133	125	121
# at risk (Late integrated)	180	164	153	148	138	134	129	126	124	119

Figure 2.
Kaplan Meier survival curves for combined AIDS and mortality by early and late integrated therapy groups for tuberculosis-HIV co-infected patients with a) CD4+ count <50 cells/mm^3 and b) CD4+ counts ≥50 cells/mm^3.

Table 1

Baseline characteristics of the patients in the SAPIT trial*

Variable	Early integrated-therapy group (N =214)	Late integrated-therapy group (N = 215)	Total (N = 429)	p-value
	Number (%)	Number (%)	Number (%)	
Age –year				0.75
Mean Range	34.3 ± 8.0 19 – 63	34.5 ± 8.7 21 – 72	34.4 ± 8.4 19–72	
Male sex	97 (45.3)	112 (52.1)	209 (48.7)	0.18
Educational level[γ]				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)	
Secondary complete	73 (34.3)	57 (26.6)	130 (30.4)	
Employed	135 (63.1)	117 (54.4)	252 (58.7)	0.08
History of tuberculosis	80 (37.4)	68 (31.6)	148 (34.5)	0.22
Karnofsky score				0.84
100 or 90	123 (57.5)	128 (59.5)	251 (58.5)	
80 or 70	86 (40.2)	81 (37.7)	167 (38.9)	
< 70	5 (2.3)	6 (2.8)	11 (2.6)	
WHO stage 4 at baseline[§]	14 (6.5)	11 (5.1)	25 (5.8)	0.54
Presence of extra-pulmonary tuberculosis	10 (4.7)	9 (4.2)	19(4.4)	0.82
Presence of resistance to tuberculosis drugs: n/N (%)				
Isoniazid Rifampin Ethambutol	13/102 (12.7) 8/102 (7.8) 1/101 (1.0)	5/101 (5.0) 4/101 (4.0) 0/100 (0.0)	18/203 (8.5) 12/203 (5.7) 1/201 (0.5)	0.08 0.37 1.00
Presence of multi-drug resistant tuberculosis	6/106 (5.7)	3/101 (3.0)	9/207 (4.4)	0.50
	Median (interquartile range)	Median (interquartile range)		
CD4+ count,-cells/mm^3[†]	154.5 (75 to 261)	149 (77 to 244)	150.0 (77 to 254)	0.93
log viral load copies/ml [‡]	5.13 (4.5 to 5.6)	5.23 (4.5 to 5.6)	5.17 (4.5 to 5.6)	0.53
Number of days on tuberculosis therapy at randomization	9 (7–13)	9 (7–14)	9 (7–14)	0.49

[γ] Educational level was not available for 1 patient in each of the groups

[*] Plus–minus values are means ±Standard Deviation.

[†] Patients underwent randomization on the basis of the CD4+ count at screening (criterion for study enrollment, <500 cells per cubic millimeter). However, for 16 patients, the CD4+ count at enrollment was 500 cells per cubic millimeter or higher.

[‡] Baseline viral load was not available for 16 patients in each of the groups

[§] The remainder of patients had stage 3 infection, according to criteria of the World Health Organization (WHO).

Table 2

Mortality, AIDS defining illness and mortality combined and immune reconstitution inflammatory syndrome rates, stratified according to baseline CD4+ cell count.

CD4+ count	Early Integrated Therapy				Late Integrated Therapy				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)		
Mortality										
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
<50 cells/mm^3	37	47.5	3	6.3 (1.3 – 18.5)	35	43.1	7	16.2 (6.5 – 33.5)	0.39 (0.06 – 1.70)	0.17
≥50 cells/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
<50 cells/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
≥50 cells/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
Immune Reconstitution Inflammatory Syndrome										
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
<50 cells/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
≥50 cells/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

Table 3

Clinical Outcomes of Tuberculosis and Antiretroviral Therapy in the SAPIT trial.

Tuberculosis treatment outcomes				
	CD4 < 50 (number (%))		**CD4 ≥ 50 (number (%))**	
	Early integrated group (N = 37)	**Late integrated group (N = 35)**	**Early integrated group (n = 177)**	**Late integrated group (n = 180)**
Tuberculosis cured[†]	23 (62%)	24 (69%)	108 (61%)	114 (63%)
Tuberculosis treatment successfully completed[‡]	8 (22%)	4 (11%)	32 (18%)	34 (19%)
Treatment success[δ]	**31 (84%)**	**28 (80%)**	**140 (79%)**	**148 (82%)**
Died prior to tuberculosis treatment completion	3 (8%)	4 (11%)	11 (6%)	7 (4%)
Treatment interruption	0 (0%)	1 (3%)	5 (3%)	3 (2%)
Failure on first line regimen	1 (3%)	0 (0%)	5 (3%)	2 (1%)
Loss to follow-up prior to tuberculosis treatment outcome	1 (3%)	1 (3%)	12 (7%)	15 (8%)
Transferred to other clinics Tuberculosis treatment outcome not known	1 (3%)	1 (3%)	4 (2%)	5 (3%)
HIV treatment outcomes				
	Early integrated group Number/total number Percent (95% CI)		**Late integrated group Number/total number Percent (95% CI)**	**p-value**
Viral load <400 copies/ml at:				
6 month after-ART initiation:				
Overall	161/179		166/179	0.45
	89.9% (84.3 – 93.8)		92.7% (87.6; 95.9)	
CD4 count < 50	30/34		32/35	0.71
	88.2% (71.6 – 96.2)		91.4% (75.8 – 97.8)	
CD4 count ≥ 50	131/145		134/144	0.52
	90.3% (84.0 – 94.4)		93.1% (87.3 – 96.4)	
12 months after-randomization:				
Overall	147/159		130/147	0.25
	92.5% (86.9; 95.9)		88.4% (81.9; 92.9)	
CD4 count < 50	30/32		23/27	0.40
	93.8% (77.8 – 98.9)		85.2% (65.4 – 95.1)	
CD4 count ≥ 50	117/127		107/120	0.51
	92.1% (85.6 – 96.0)		89.2% (81.9 – 93.9)	
18 months after-randomization:				
Overall	144/153		135/143	1.00
	94.1% (88.8; 97.1)		94.4% (88.9; 97.4)	

Tuberculosis treatment outcomes				
	CD4 < 50 (number (%))		CD4 ≥ 50 (number (%))	
	Early integrated group (N = 37)	Late integrated group (N = 35)	Early integrated group (n = 177)	Late integrated group (n = 180)
CD4 count < 50	28/30		25/26	1.00
	93.3% (76.5 – 98.8)		96.2% (78.4 – 99.8)	
CD4 count ≥ 50	116/123		110/117	.1.00
	94.3% (88.2 – 97.5)		94.0% (87.6 – 97.4)	
Mean CD4+ count increase from baseline – cells/mm^3 at				
	mean increase (95% CI, N)		**mean increase (95% CI, N)**	
At 6 months post-antiretroviral therapy initiation:				
Overall	132.4		131.6	0.95
	(113; 152, n=178)		(111; 152, n=179)	
CD4 count < 50	124.0 (94; 154, n = 34)		103.6 (83; 124, n = 35)	0.25
CD4 count ≥ 50	134.5 (111; 157, N = 144)		138.4 (113; 163, n = 144)	0.82
12 months after-randomization:				
Overall	183.1 (162; 204, n=159)		124.7 (105; 145, n=147)	0.009
CD4 count < 50	170.1 (127; 213, n = 32)		111.0 (81; 141, n = 27)	0.03
CD4 count ≥ 50	186.4 (163; 210, n = 127)		127.8 (104; 152, n = 120)	0.001
18 months after-randomization:				
Overall	217.4 (192; 243, n=152)		172.2 (150; 194, n=142)	0.009
CD4 count < 50	206.8 (166; 248, n = 30)		172.6 (134; 212, n = 26)	0.22
CD4 count ≥ 50	220.0 (189; 251, n = 122)		172.1 (146; 198, n = 116)	0.02

†Tuberculosis cure was in accordance with the 2004 South African National tuberculosis Control Program Guideline, which states that "a patient who is smear-negative at, or one month prior to, the completion of treatment and 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 therapy was defined as the use of more than 85% of the prescribed medication.

δTreatment success is defined as Tuberculosis cure and successful tuberculosis treatment completion

§Therapy failure was defined as the presence of a positive smear or culture for Mycobacterium tuberculosis obtained at least 5 months after the initiation of tuberculosis therapy.