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Changes to antiretroviral drug regimens during integrated TB-HIV treatment: Results of the SAPiT trial

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Abstract

Background—Frequency of drug changes in combination antiretroviral therapy among patients starting both tuberculosis (TB) and human immunodeficiency virus (HIV) therapy, as a result of treatment-limiting toxicity or virological failure, is not well established.

Methods—Patients in the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) trial were randomized to initiate antiretroviral therapy either early or late during TB treatment or after completion of TB treatment. Drug changes due to toxicity (defined as due to grade 3 or 4 adverse events) or virological failure (defined as viral load > 1000 copies/ml on two occasions, taken at least 4 weeks apart) were assessed in these patients.

Results—A total of 501 TB-HIV co-infected patients were followed for a mean of 16.0 (95% confidence interval (CI): 15.5 to 16.6) months after antiretroviral therapy (ART) initiation. The standard first-line ARVs used, were efavirenz, lamivudine and didanosine. Individual drug switches for toxicity occurred in 14 patients (incidence rate: 2.1 per 100 person-years; 95% (CI): 1.1 to 3.5), and complete regimen changes due to virological failure in 25 patients (incidence rate: 3.7 per 100 person-years; CI: 2.4 to 5.5). The most common treatment limiting toxicities were neuropsychiatric effects (n=4; 0.8%), elevated transaminase levels and hyperlactatemia (n= 3; 0.6%), and peripheral neuropathy (n=2; 0.4%). Complete regimen change due to treatment failure was more common in patients with CD4+ cell count <50cells/mm^3 (p<0.001) at ART initiation and body mass index greater than 25 kg/m^2 (p=0.01) at entry into the study.

Conclusion—Both drug switches and complete regimen change were uncommon in patients co-treated for TB-HIV with the chosen regimen. Patients with severe immunosuppression need to be monitored carefully, as they were most at risk for treatment failure requiring regimen change.

Introduction

There were an estimated 8.7 million cases of tuberculosis (TB) in 2011, approximately 1.1 million of which were co-infected with human immunodeficiency virus HIV [1]. Sub-

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Saharan Africa accounted for 80% of the global burden of TB–HIV co-infections [1]. Co-treatment of these diseases presents several management challenges. Treatment-limiting toxicity is an important concern when integrating TB-HIV treatment. Other concerns include drug interactions between rifampicin and some classes of antiretrovirals [2], immune reconstitution inflammatory syndrome (IRIS) and high pill burden [3, 4].

These clinical challenges potentially undermine the success of both HIV and TB control programs, contribute to the poor tolerability of combined antiretroviral therapy (ART) and TB therapy, and impact on treatment adherence. There is now evidence that initiating ART during TB therapy in co-infected patients significantly reduces mortality, and improves outcomes in both conditions [5–8]. However, these benefits need to be weighed against the risks of morbidity due to treatment interruptions, toxicity or treatment failure.

There are limited prospective data from randomized controlled trials available to inform clinical guidelines. In this paper we report the incidence, predictors of, and reasons for ART changes, in a cohort of TB-HIV co-infected patients enrolled in a randomized controlled trial designed to determine the optimal time to initiate ART in TB treatment.

Methods

Study Design and Participants

The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) trial was an open label, three-arm, randomized, controlled trial, which enrolled 642 patients between June 2005 and July 2008, to determine the optimal timing of ART initiation in TB-HIV co-infected patients. Details of the study design and procedures and the primary outcomes of the study have been described previously [5, 6]. In brief, TB-HIV co-infected patients, aged 18 years or older (screening CD4+ count < 500 cells/mm^3), were enrolled at the CAPRISA eThekwini clinical research site, which adjoins the Prince Cyril Zulu Communicable Disease Centre (PCZCDC), in Durban, South Africa. HIV-infection was confirmed by two rapid HIV tests and pulmonary TB (PTB) was confirmed by acid fast bacilli smear positivity.

Study Procedures

Patients were randomized to initiate ART within 4 weeks of tuberculosis treatment initiation (early integrated treatment arm), within 4 weeks after completion of intensive phase of tuberculosis treatment (late integrated treatment arm), or within 4 weeks after tuberculosis therapy completion (sequential treatment arm). Patients were initiated on a once daily ART regimen consisting of efavirenz 600mg, lamivudine 300mg and enteric-coated didanosine 250mg (weight <60kg) or 400mg (weight ≥ 60kg). All first episode PTB was treated with a fixed–dose combination of rifampicin, isoniazid, ethambutol and pyrazinamide according to pre-treatment weight for 2 months (intensive phase), with subsequent fixed-dose combination of isoniazid and rifampicin for 4 months (continuation phase). Patients with re-treatment PTB received a 60-day intensive phase which included streptomycin, followed by a 100-day continuation phase, in accordance with the national policy. Patients were offered community- or clinic-based directly observed therapy. All patients received a standard package of care which included adherence counseling and cotrimoxazole prophylaxis. Additionally, female patients were required to use hormonal contraception while on efavirenz.

Follow-up visits for the monitoring of safety, clinical status and adherence to ART were scheduled monthly for 24 months. Laboratory investigations included baseline (at screening and enrolment) CD4+ cell count using a FACS flow cytometer (Becton Dickinson, Franklin Lakes NJ, USA), viral load by HIV RNA PCR (Roche Cobas Amplicor HIV-1 Monitor

v1.5-lower limit of detection 400 copies/ml), full blood counts, urea, electrolytes, creatinine, liver function, Hepatitis B surface antigen tests and syphilis serology. These investigations were done at baseline and repeated every 6 months or earlier, if clinically indicated. ART adherence was assessed monthly using pharmacy pill counts. Pillcounts were assessed based on the number of pills dispensed and physically returned. In addition we took into account lost doses and remaining doses reported on previously that may have been returned at a subsequent visit.

Adverse events were graded with the use of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0) [9]. A toxicity grading of 3 or 4 was used as indication for discontinuation or substitution of specific antiretroviral drugs, and referred to as drug switch due to toxicity. Drug switch could also occur as a result of contraindication or drug interaction.

Virological failure, defined as a viral load > 1000copies/ml on two occasions, taken at least 4 weeks apart, resulted in discontinuation or complete regimen change of all first line ART drugs. Viral suppression or undetectable viral load was defined as a viral load of < 400 copies/ml. Drug changes therefore referred to both individual drug switches, as a result of toxicity, and to complete regimen changes, as a result of virological failure. The most commonly utilised (72%) second line regimen in patients requiring complete regimen change comprised, lopinavir/ritonavir, tenofovir and zidovudine.

Study Oversight

Ethical approval for the study was provided by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (E107/05), and the Medicines Control Council of South Africa (MCC Ref: 20060157).

Statistical analysis

This analysis was based on a 24 months post randomization follow-up time period to allow for the patients in the sequential treatment arm to have sufficient time on antiretroviral therapy to be comparable to the other two arms.

Time at risk was calculated from ART initiation to the date on which drugs were stopped, death, withdrawal or termination from the study. For patients who changed drugs more than once, only the first change was included in the incidence rate calculation. Confidence intervals (CI) for incidence and incidence rate ratios (IRR) assumed a Poisson distribution. Multivariate Cox proportional hazards regression models were used separately for drug switch and complete regimen change to assess the risk factors for regimen changes. Data published in 2010 [5] provided interim results following the September 2008 safety monitoring committee review. Results presented in 2011 were based on the complete set of trial data [6]. The data presented in this paper, in addition, cover the full 24-month follow-up period post randomization. All statistical tests were two sided. Fisher's Exact test or Fisher-Freeman-Halton test was used for the analysis of categorical data. The T-test for independent samples, Wilcoxon two-sample, one way ANOVA or the Kruskal-Wallis tests were used for the analysis of continuous data. Statistical analysis was done using SAS (version 9.2.; SAS Institute Inc., Cary, NC, USA).

Results

Of 1331 patients screened for eligibility, 642 were enrolled and randomized into the study, with 501 initiating ART; 198 (92.5%); 164 (76.3%); 139 (65.3%) in the early integrated, late integrated and sequential arms respectively (Figure 1). Patients were followed for an average of 17.6 (95% CI: 16.6 to 18.6); 16.8 (95% CI: 16.0 to 17.6) and 13.0 (95% CI: 12.3 to 13.7)

months after ART initiation, with a retention rate at 24 months post randomization of 76.6%, 71.2% and 71.3%, in the early integrated, late integrated and sequential arms respectively.

Baseline results

There were differences only for weight (p=0.01) and haemoglobin (p<0.001) across the three treatment arms, and CD4+ cell counts were lower in in patients who had drug changes (p=0.01) (Table 1). At baseline, the proportion of patients with Hepatitis B surface antigenaemia, peripheral neuropathy and raised transaminases-(≥5 times the upper limit of normal) were similar across the three treatment arms (Table 1).

Incidence of complete regimen change and drug switch across the three treatment arms

ART changes occurred in 39/501 patients, with an incidence rate (IR) of 5.8 (95% CI: 4.1 to 8.0) per 100 person-years (py). One participant experienced two individual drug switches for different reasons. Among14/501 (2.8%) patients, drug switches for toxicity occurred at a median time of 3.6 months (IQR: 2.5 to 6.9) post ART initiation, with an incidence rate of 2.1 (95% CI: 1.1 to 3.5). Complete regimen change occurred in 25/501 (5.0%), with an incidence rate of 3.7 (95% CI: 2.4 to 5.5) per 100 py. There was no significant difference in the incidence of individual drug switches or complete regimen changes between the three arms (p=0.25). There were no differences in median time to single drug switches (p=0.64) and complete regimen changes (p=0.86) across the three treatment arms. Incidence of complete regimen changes in the early integrated treatment arm was 2.3 per 100 py (95% CI: 0.9 to 4.8) compared to 3.9 per 100 py (95% CI: 1.8 to 7.4) in the late integrated treatment arm (IRR: 0.6; 95% CI: 0.2 to 1.8; p=0.37) and 5.9 per 100 py (95% CI: 2.7 to 11.1) in the sequential treatment arm (IRR: 0.4; (95% CI: 0.1 to 1.2; p=0.19) (Table 2). In patients with CD4+ cell counts < 50cells/mm^3, the incidence of complete regimen change was 5.5 (95% CI: 1.1 to 16.1), 12.9 (95% CI: 4.7 to 28.2) and 13.4 (95% CI: 2.8–39.3) per 100 py in the early integrated, late integrated and sequential treatment arms respectively (p=0.53). In patients with CD4+ count> 50cells/mm^3, the incidence of complete regimen change was 1.6 (95% CI: 0.4 to 4.2), 1.6 (95% CI: 0.3 to 4.8 and 4.6 (95% CI: 1.7 to 10.0) per 100 py in the early integrated, late integrated and sequential treatment arm, respectively (p=0.17).

Reasons for drug switches

The reasons for and time to individual drug switches from ART initiation are shown in Table 3. We found the most common treatment-limiting toxicities to be neuropsychiatric effects (n=4; 0.8%) elevated transaminases and hyperlactatemia (n= 3; 0.6%) and peripheral neuropathy (n=2; 0.4%). Eleven of the 15 drug switches occurred within the first 6 months after ART initiation. Among the 14 patients with drug switches, five were on concurrent TB-HIV treatment. Five patients in each of the early and late treatments arms and one in the sequential treatment arm experienced ART treatment interruptions due to toxicity, but these toxicities did not lead to any drug switches.

Complete Regimen Change

The median time to complete regimen change from ART initiation was 9,9 (IQR: 6.4 to 13.0), 10.4 (IQR: 9.7 to 11.0), 9.5 (IQR: 8.1 to 10.9) months with no significant difference between the arms (p=0.64). Among the patients with complete regimen change none were on concurrent TB therapy at the time of regimen change. The median viral load before complete regimen change was 4.9 (IQR: 4.3 to 5.6) log copies/ml. Virologic suppression rates were high in all treatment arms after 18 months of follow-up [5, 6].

Adherence

The overall adherence at 24 months post ART initiation, based on pill count data, was similar across the 3 treatment arms (p=0.64). Among patients with drug changes, the adherence rates were 90.4%, 86.2% and 93.6% (p=0.58), whereas among patients with no drug changes, the adherence rates were 95%, 96% and 97.4% in the early, late and sequential treatment arms, respectively (p=0.48).

Risk factors associated with drug switches and complete regimen change in co-treated patients

Treatment arm was not associated with drug switches and complete regimen changes. Baseline CD4+ cell count < 50 cells/mm^3 was significantly associated with complete regimen change (HR: 4.7; 95% CI: 1.6 to 14.0; p=0.005) compared to CD4+ cell count ≥50 cells/mm^3. Additionally, patients with a BMI greater than 25 kg/m^2 were more likely to experience complete regimen change (HR: 3.3; 95% CI: 1.4–7.8; p=0.01) compared to patients with BMI 18.5–25 kg/m^2. (Table 4)

Discussion

We demonstrated similar incidence of ART drug switches irrespective of the timing of ART initiation relative to the start of TB treatment, providing evidence that potentiated drug toxicity may be of limited concern in TB-HIV co-treatment. Low rates of drug switching due to toxicity was observed in all three arms, with no significant difference in the incidence of drug switching between the treatment arms, although the number of drug switches was higher in the early and late integrated compared to the sequential treatment arm. The regimen chosen for this study provided a once-daily option at a time before the availability of tenofovir, to be taken with once daily TB treatment. Reports from two other randomised controlled trials also show similar rates of toxicity in patients who start ART early (within 2 weeks), or later (within 8 weeks), in the course of TB treatment. In the STRIDE study, 44% and 47% of patients experienced grade 3 and 4 adverse events, with 14/405 patients in the early group; and 7 /401 patients in the late-ART group switching ART regimen for toxicity, respectively [7]. Likewise, the CAMELIA study found similar incidence of drug-related adverse events; 2.93 (95% CI, 2.58 to 3.32) and 3.21 (95% CI, 2.83 to 3.63) events per 100 person months in the earlier and later ART groups respectively [8]. The first line ARV treatment regimen used in the STRIDE and CAMELIA studies, included once daily efavirenz, emtricitabine and tenofovir and efavirenz, lamivudine and stavudine taken twice daily, respectively.

Data on rates of adverse events and drug switches due to toxicity in patients receiving therapy for both HIV and tuberculosis are limited. Observational studies in TB-HIV co-treatment demonstrate conflicting rates of drug related adverse events, compared to evidence to the contrary from the three relatively large randomized controlled trials. 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 TB [10]. However, retrospective studies conducted in Thailand and India, among patients with CD4 < 100 cells/mm^3, found drug-related adverse events occurred in 66.1% of co-treated patients in the first 2 months of TB treatment [11], and that concomitant use of ART and TB treatment was a predictor of adverse events (OR: 1.88) [12]. Notably, in these two relatively small studies (< 150 patients), two third of all patients received a NVP-containing ART regimen, whereas almost all of our patients were initiated on an EFV-based ART regimen.

Previous studies have shown that peripheral neuropathy (43%) and hepatoxocity (5–10%) are the most common toxicities in patients receiving TB-HIV co-treatment [7, 13–15]. The

most common cause of drug switching in our study was neuropsychiatric toxicity, most likely related to the use of an EFV-based first line regimen. Contrary to other studies, describing the increased risk of hepatotoxicity when ART is introduced during the intensive phase of TB therapy [15], there were no drug switch for treatment limiting hepatotoxicity among patients in the early integrated treatment arm. However, drug switch for hepatotoxicity was observed in the late integrated and sequential treatment arms. This may be as a result of patients having lower CD4+ cell counts due to delay in initiation of ART[15]. While studies that report an increased risk of hepatotoxicity in TB-HIV co-treatment cite baseline elevated transaminases and hepatitis B antigenaemia as likely risk factors [16–25], the prevalence of both conditions was low in our study, which may account for the small number of drug switch from hepatotoxicty that were observed.

It is likely that the profile of toxicities presenting in this cohort is linked to our choice of first line ART regimen, which was chosen for its suitability to be co-administered with directly observed TB treatment and once daily dosing. The absence of clinically significant alteration of efavirenz plasma concentration when co-administered with rifampicin has been demonstrated [26, 27]. Efavirenz has also been shown to have a lower risk of hepatotoxicity than nevirapine [25]. Enteric coated didanosine (ddI-EC) has a lower risk of peripheral neuropathy and gastro-intestinal toxicities than stavudine and buffered ddI [14], the available NRTIs at the time of study conduct.

In addition, this study was conducted in ambulant, relatively clinically stable patients with TB disease mainly confined to the lungs. Although other nucleoside/nucleotide reverse transcriptase options, included in fixed-dose combinations, have now eclipsed didanosine-containing regimens as the first-line options, enteric-coated didanosine may still provide a useful alternative in patients unable to tolerate the alternative once-daily options[28].

Despite the additional pill burden when TB and ART therapy was co-administered in the early and late integrated treatment arms, the adherence was similar across the three treatment arms. The incidence of ART complete regimen change from virological failure was low and did not differ by treatment arm, despite the addition of 3 ARVs to the 4-drug intensive phase of TB or to the 2 drug maintenance phase of TB therapy. Similar high rates of virological suppression were achieved and sustained, through to 18 months of follow-up after ART initiation across all study arms. These rates were similar to rates achieved at 48 and 50 weeks in the STRIDE and CAMELIA studies respectively [7, 8], and better than reports of virological suppression rates (76%) achieved in treatment programmes from sub-Saharan Africa at 12 months [29].

The higher incidence of complete regimen change in patients with CD4 <50cells/mm^3 observed in this study has also been reported in other TB and non-TB settings [30–33]. Several studies have shown that low CD4+ cell counts are a predictor for complete regimen change due to virological failure. [34–36]. The drug switches in patients will low CD4+ cell counts may not be directly associated with TB HIV co-treatment, but may instead be due to the presence of other co-morbidities in patients with advanced HIV disease.

Low BMI has been shown in previous studies to be associated with poor treatment outcomes and a potential predictor of treatment failure in resource constrained settings [34–36]. In contrast our study found higher BMI >25 $kg/m^{2,}$ to be associated with a higher risk of complete regimen change, this may in part, be explained by findings from other studies which found sub-therapeutic drug levels [37] and BMI > 25 kg/m^2 to be an independent risk factor for virological failure [38]

The following study limitations need to be considered. We included ambulant patients with CD4+cell count up to 500 cells mm^3, higher than the CD4 threshold for ART in current

WHO and South African ART treatment guidelines. The inclusion of patients less advanced in the course of their HIV disease may have led to an under-estimation of the true effect of additive toxicity when co-treating TB-HIV. In this study, ART drug switches were triggered by grade 3 or 4 toxicities. However, grade 1 and 2 toxicities may affect adherence to therapy or patients' quality of life. Interruptions to TB drug therapy are also not included in this analysis. Pillcount as a measure of adherence reported in this study, may have over-estimated the adherence reported.

Conclusion

Both drug switches and complete regimen changes were uncommon in patients co-treated for TB-HIV, using a didanosine, lamivudine and efavirenz first-line regimen. Manageable treatment-limiting toxicities occurred early, and affected a small percentage of the trial participants. The survival benefit from early initiation of ART in TB-HIV co-infected patients outweighed the concerns of treatment-limiting toxicities. Low CD4 count and higher BMI (>25), at baseline increased the risk of treatment failure and complete regimen change, although the association with higher BMI may need further validation.

Patients with severe immunosuppression need to be monitored carefully, using viral load determinations, as they were most at risk for treatment failure requiring regimen change. The additional pill burden with combined TB-HIV treatment did not have a significant effect on adherence to ART in this study. These data further strengthen the available evidence of the benefits of integrating TB-HIV treatment and underline the continued usefulness of alternative once-daily regimens in such settings.

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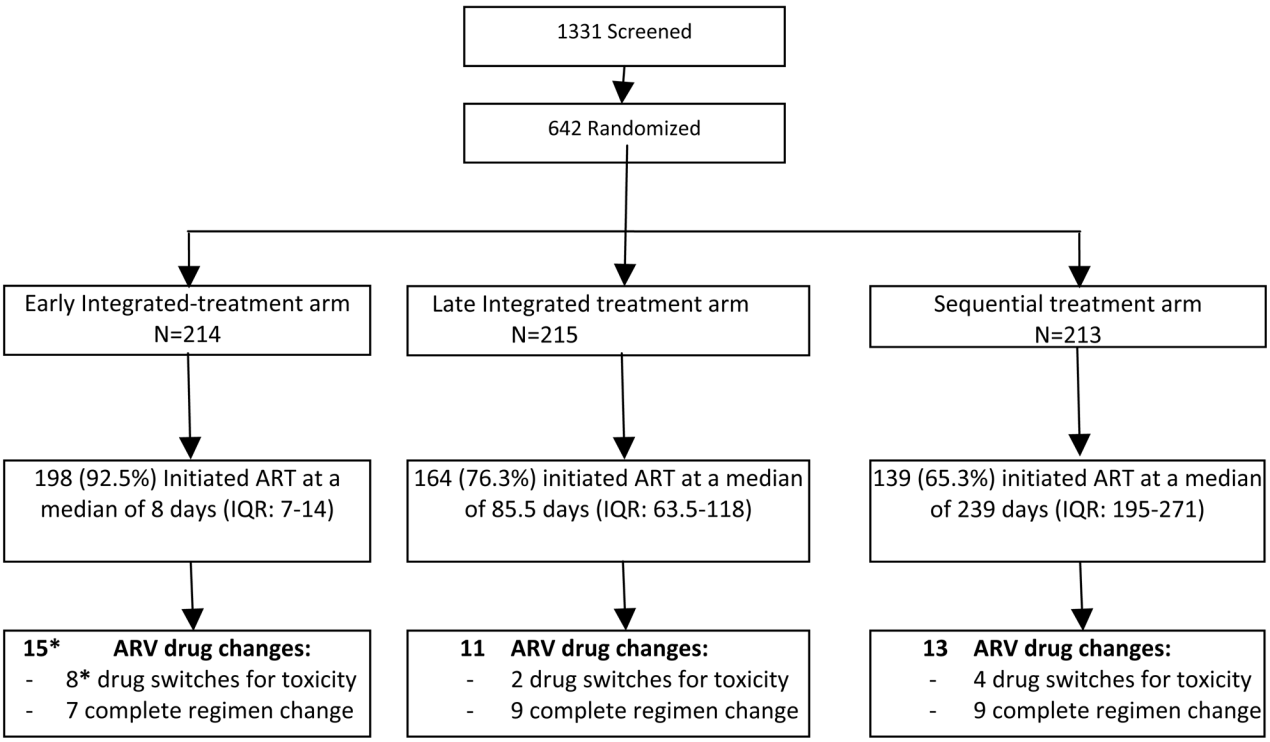

Figure 1.

SAPiT trial: Screening, randomization, and follow-up of study participants, demonstrating distribution of patients with drug switches due to toxicity and complete regimen change due to virological failure

*1 patient experienced 2 individual drug switches due to toxicity for different reasons in the early integrated arm (9 drug switches and 16 ARV drug changes in total) but only the initial drug switch is illustrated in this figure and used in the incidence rate calculation.

Table 1

Baseline Characteristics for Patients Initiated on ART

Characteristic	Early integrated treatment arm (N=198)	Late integrated treatment arm (N=164)	Sequential treatment arm (N=139)	p-value	Participants without ART changes (N=462)	Participants with ART changes (N=39)	p-value
Mean age(SD), years	34.6 (8.1)	35.1 (9.1)	34.8 (9.5)	0.86	34.9 (8.7)	35.1 (6.8))	0.81
Male, n (%)	90 (45.5)	79 (48.2)	68 (48.9)	0.79	221 (47.9)	16 (41.0)	0.50
WHO stage 4, n (%)	13 (6.6)	11 (6.7)	8 (5.8)	0.95	29 (6.3)	3 (7.7)	0.73
Past history of tuberculosis, n (%)	73 (36.9)	49 (29.9)	43 (30.9)	0.31	154 (33.4)	11 (28.2)	0.50
Median CD4+ (IQR), cells/mm^3 *a,b*	145.5 (73–267)	141 (57.5–247)	146 (74–260)	0.60	150 (82–253)	65(27–215)	0.01
Mean log_{10} HIV RNA (SD), copies/ml *b, c*	5.0 (0.9)	5.0 (0.9)	5.0 (0.8)	0.98	5.0 (0.9)	5.2 (0.9)	0.27
Mean haemoglobin (SD), g/dl *b,d*	10.6 (2.0)	11.5 (1.8)	12.0 (2.0)	<0.001	11.3 (2.0)	11.3 (1.8)	0.87
Mean weight (SD), kg *b,e*	59.6 (10.5)	61.7 (10.7)	62.9 (11.5)	0.01	61.0 (10.9)	62.2 (10.8)	0.51
Body mass index *e*				0.45			0.06
<18.5 kg/m^2, n (%)	18 (9.1)	10 (6.1)	7 (5.1)		32 (7.0)	3 (7.7)	
18.5–25 kg/m2, n (%)	132 (66.7)	105 (64.0)	88 (64.2)		306 (66.5)	19 (48.7)	
>25 kg/m^2, n (%)	48 (24.4)	49 (29.9)	42 (30.7)		122 (26.5)	17 (43.6)	
Past history of alcohol use, n (%) *f*				0.81			0.44
Never	159 (84.6)	138 (85.7)	110 (82.1)		374 (83.9)	32 (88.9)	
Occasionally	23 (12.3)	16 (9.9)	17 (12.7)		54 (12.1)	2 (5.6)	
Frequently	6 (3.2)	7 (4.4)	7 (5.2)		18 (4.0)	2 (5.6)	
First line regimen, n (%) *g*							
EFV, 3TC, ddI	195 (98.5)	162 (98.8)	134 (97.1)	0.59	455 (98.7)	36 (92.3)	0.03
NVP, 3TC, ddI/ EFV, 3TC, AZT	3 (1.5)	2 (1.2)	4 (2.9)		6 (1.3)	3 (7.7)	
Presence of peripheral neuropathy before ART initiation, n(%)	6 (3.0)	6 (3.7)	2 (1.4)	0.52	13 (2.8)	1 (2.6)	1.00
Hepatitis B surface antigen, n(%) *b,h*				0.80			1.00
Positive	15 (9.4)	11 (7.3)	11 (8.3)		34 (8.4)	3 (8.3)	
Negative	144 (90.6)	139 (92.7)	122 (91.7)		372 (91.6)	33 (91.7)	
ALT≥ 5xULN, IU/L	1 (0.5) (n=197)	0 (n=164)	0 (n=137)		1(0.2) (n=459)	0	0
AST≥5xULN, IU/L	2 (1.0) (n=197)	2 (1.2) (n=164)	0 (n=137)	0.57	3 (0.7) (n=459)	1 (2.6) (n=39)	0.28

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SD-standard deviation; IQR-Interquartile range; BMI-Body mass index; AST-aspartate aminotransferase; ALT-alanine transaminase

[a] 1 participant had missing CD4+ count in the sequential arm

[b] At ARV initiation

[c] 6 participants in the early integrated treatment arm, 1 in the late integrated treatment arm and 2 in the sequential treatment arm had missing viral load

[d] 2 participants in the early integrated treatment arm, 2 in the late integrated treatment arm and 3 in the sequential treatment arm haemoglobin

[e] 2 participants in the late integrated treatment arm do not have weight, missing data not included in percentage calculation

[f] 10 participants in the early integrated treatment arm, 3 in the late integrated treatment arm and 5 in the sequential treatment arm had missing past history of alcohol use

[g] 1 participant in the sequential arm had no regimen data

[h] 39 participants in the early integrated treatment arm, 14 in the late integrated treatment arm and 6 in the sequential treatment arm had missing hepatitis data

Table 2

Incidence rate of drug switches and compete regimen change across the 3 treatment arms

	Early integrated treatment am			Late integrated treatment am			Sequential treatment am				Early vs late	Early vs sequential	Late vs sequential
	Person-Years (n)	No. Of switches	Incidence Rate / 100 Person-Years (95% CI)	Person-Years (n)	No. Of switches	Incidence Rate / 100 Person-Years (95% CI)	Person-Years (n)	No. Of switches	Incidence Rate / 100 Person-Years (95% CI)	p-value	IRR (95%CI); p-value	IRR (95%CI); p-value	IRR (95%CI); p-value
Drug change [a]	290.4 (198)	15	5.2 (2.9–8.5)	229.3 (164)	11	4.8 (2.4–8.6)	150.0 (139)	13	8.7 (4.6–14.8)	0.54	1.1 (1.5–2.6); 0.70	0.6 (0.3–1.4); 0.55	0.6 (0.2–1.3); 0.21
Drug switch	290.4 (198)	8	2.8 (1.2–5.4)	229.3 (164)	2	0.9 (0.1–3.2)	150.0 (139)	4	2.7 (0.7–6.8)	0.25	3.2 (0.6–30.5); 0.09	1.03 (0.3–4.7); 0.56	0.3 (0.03–2.3); 0.30
Complete regimen change	300.1 (198)	7	2.3 (0.9–4.8)	230.6 (164)	9	3.9 (1.8–7.4)	153.3 (139)	9	5.9 (2.7–11.1)	0.32	0.6 (0.2–1.8); 0.37	0.4 (0.1–1.2); 0.19	0.7 (0.2–1.9); 0.44

[a] combination of drug switches and complete regimen change

Table 3

Summary of ART changes

Drug switched and Reason for Switch	Number of switches (Months to switch [a])			
	Summary of Drug Switches: N=15 (occurring in 14 patients)			
	Early integrated treatment arm	Late integrated treatment arm	Sequential treatment arm	Total
Didanosine (ddI) N=5				
Peripheral neuropathy	2 (10.9 and 1.0)	0	0	2 (10.9 and 1.0)
Hyperlactatatemia	1(12.3)	0	0	1 (12.3)
Pancreatitis, hepatomegaly	0	1 (3.1)	0	1 (3.1)
Acute viral Hepatitis	0	0	1 (3.2)	1 (3.2)
Efavirenz (EFV) N=5				
Neuropsychiatric	3 (0.5, 2.5 and 3.6)	0	1 (5.6)	4 (0.5, 2.5,3.6 and 5.6)
Rash	0	0	1 (0.5)	1 (0.5)
Zidovudine (AZT) N=2				
Anaemia	0	1 (8.3)	0	1 (8.3)
Hyperlactatatemia	1 (2.4)	0	0	1 (2.4)
Nevirapine (NVP) N=2				
Hypersensitivity	1 (6.9)	0	0	1 (6.9)
Recurrent tuberculosis	0	0	1 (5.3)	1 (5.3)
Didanosine (ddI) and Lamivudine(3TC) N=1				
Severe anaemia	1 (3.7)	0	0	1 (3.7)
Changes to Second Line Drugs, Complete Regimen Change (CRC) N=25				
EFV/3TC/ddI				
Virological failure	7 [9.9 (6.4–13.0)]	9 [10.4 (9.7–11.0)]	9 [9.5 (8.1–10.9)]	25 [10.2 (8.1–11.0)]

[a] Median (IQR) for 25 that changed to second line due to virological failure

Table 4

Risk factors for drug switch and complete regimen change

Variable	Drug switch for toxicity				Complete regimen change for virologic failure			
	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Randomization arm								
Sequential treatment arm	reference		reference		reference		reference	
Early integrated treatment arm	1.4 (0.4–4.8)	0.55	0.9 (0.2–3.3)	0.83	0.5 (0.2–1.3)	0.14	0.5 (0.2–1.5)	0.24
Late integrated treatment arm	0.4 (0.1–2.6)	0.31	0.4 (0.1–2.1)	0.25	0.7 (0.3–1.9)	0.51	0.6 (0.2–1.6)	0.35
Sex								
Male	reference		reference		reference		reference	
Female	2.3 (0.7–7.2)	0.17	2.0 (0.5–7.9)	0.32	0.9 (0.4–2.1)	0.89	0.8(0.4–2.0)	0.71
Age (per 1 year increase)	0.99 (0.9–1.1)	0.67	0.97(0.9–1.1)	0.48	1.01 (0.97–1.1)	0.61	1.0(0.9–1.0)	0.79
CD4+ cell count (cells/mm^3)[a]								
<50	1.2 (0.3–4.4)	0.77	1.3 (0.3–6.5)	0.74	4.4 (2.0–9.6)	0.0002	5.1 (2.2–11.5)	<0.001
≥50	reference		reference		reference		reference	
Body mass Index (kg/m^2)								
18.5–25	reference		reference		reference		reference	
<18.5	2.2 (0.5–10.0)	0.33	1.2 (0.1–10.2)	0.86	1.0 (0.1–8.1)	0.96	0.8 (0.1–6.6)	0.87
>25	0.8 (0.2–2.9)	0.72	0.5 (0.1–2.5)	0.38	3.5 (1.5–7.9)	0.003	3.3 (1.4–7.8)	0.01
WHO stage								
Stage 3	reference				reference			
Stage 4	1.1 (0.1–8.5)	0.92	-	-	1.3 (0.3–5.4)	0.73	1.0 (0.2–4.3)	0.99
Hepatitis B surface antigen								
Negative	reference		reference		reference		reference	
Positive	2.3 (0.5–10.9)	0.28	2.9 (0.6–14)	0.20	0.4 (0.1–3.1)	0.39	0.3 (0–2.5)	0.29

[a] at ARV initiation HR: Hazard ratio