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Early clinical and programmatic outcomes with tenofovir-based antiretroviral therapy in Zambia

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Abstract

Background—In July 2007, amid some controversy over cost, Zambia was the first African country to introduce tenofovir (TDF) as a component of first-line antiretroviral therapy (ART) on a wide scale.

Methods—We compared drug substitutions, mortality, and “programmatic failure” among adults starting TDF-, zidovudine (ZDV)-, and stavudine (d4T)-containing ART. Programmatic failure was defined as death, withdrawal, or loss to follow-up.

Results—Between July 2007 and January 2009, 10,485 adults initiated ART (66% on TDF, 23% on ZDV, 11% on d4T), with a median follow-up time of 239 days (IQR:98,385). Those starting TDF were more likely to be male and more likely to have indicators of severe disease at baseline. In adjusted Cox proportional hazards models, ZDV- (adjusted hazard ratio [AHR]=2.74, 95% CI=2.30-3.28) and d4T-based regimens (AHR=1.92, 95% CI=1.55-2.38) were associated with higher risk for drug substitution when compared to TDF-based regimens. Similar hazards were noted for overall mortality (ZDV: AHR=0.81, 95% CI=0.62-1.06; d4T: AHR=1.03, 95% CI=0.74-1.43) and programmatic failure (ZDV: AHR=0.99, 95% CI=0.88-1.11; d4T: AHR=1.11, 95% CI=0.96-1.28) when compared to TDF.

Conclusions—TDF is associated with similar clinical and programmatic outcomes as ZDV and d4T, but appears to be better tolerated. Although further evaluation is needed, these results are encouraging and support Zambia's policy decision.

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Keywords

tenofovir; antiretroviral therapy; clinical outcomes; programmatic outcomes; Africa; Zambia

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is an important first-line agent for antiretroviral therapy (ART) in North America and Europe because of its proven effectiveness, favorable toxicity profile, and demonstrated regimen durability.¹⁻³ In contrast, introduction of TDF into first-line therapy has been limited in resource-constrained settings, particularly in sub-Saharan Africa. Although experience with the agent has been favorable within clinical trials,⁴ the cost of TDF has been a major barrier to widespread use. A one-year supply of the drug is estimated at \$221 (U.S. dollars) when prescribed with lamivudine (3TC) and nevirapine (NVP), a cost significantly higher than alternative first-line regimens incorporating zidovudine (\$153) or stavudine (\$96).⁵ The toxicities associated with TDF may also be difficult to manage in settings where simple laboratory monitoring (e.g. serum creatinine) is poorly accessible. Recent work in Zambia, for example, demonstrated that approximately one-third of individuals starting ART had some degree of renal insufficiency.⁶ Without appropriate monitoring of renal function, use of TDF could lead to iatrogenic renal failure in settings where options for management (e.g. dialysis) may be limited.

The Zambia government has implemented one of the most successful national programs for HIV care and treatment in sub-Saharan Africa. Services for HIV care and treatment have rapidly expanded, from 15,000 adults and children accessing ART in April 2004 to approximately 219,000 by December 2008 (unpublished data, A. Mwango). In July 2007, amid some donor controversy, the Zambian Ministry of Health introduced TDF as part of first-line therapy, making it the first African country to use the drug on a wide scale.⁷ By February 2009, more than 15,000 HIV-infected adults had initiated TDF-based therapy in Zambia's capital city of Lusaka, site of the country's largest ART program.^{8, 9} In this report, we describe the early outcomes among patients initiating TDF-based ART in this urban African setting.

METHODS

Clinical care in the Lusaka ART program

We analyzed programmatic data from the national HIV care and treatment program in Lusaka, Zambia.^{8, 9} This program is supported primarily by the Ministry of Health, with additional funding from the U.S. President's Emergency Plan for AIDS Relief and the Global Fund for AIDS, Tuberculosis, and Malaria. Clinical care provided across all sites has been standardized according to national protocols. Adults are enrolled and initially screened for ART eligibility. Individuals who have CD4 cell counts less than 200 cells/uL; WHO stage 4 clinical disease; or WHO stage 3 and CD4 cell counts less than 350 cells/uL are eligible for therapy. Since 2004, first-line ART has comprised a nucleoside reverse transcriptase inhibitor (NRTI) backbone – zidovudine (ZDV) or stavudine (d4T) plus lamivudine (3TC) – in combination with a non-NRTI (e.g. efavirenz [EFV] or nevirapine [NVP]). In July 2007, TDF and emtricitabine (FTC) were added as a nucleotide/nucleoside reverse transcriptase inhibitor backbone. Despite the higher cost associated with these drugs, the Ministry of Health based their decision on the TDF's favorable toxicity profile, its high genetic barrier to resistance, and its once-daily dosing schedule. Selection of a patient's first-line ART regimen is based on programmatic factors (e.g. drug availability) and medical contraindications. Because ZDV initiation is associated with clinically significant anemia,^{10, 11} individuals with baseline hemoglobin concentration < 10 g/dL are started on d4T- or TDF-based ART. The primary contraindication for TDF initiation is severe renal insufficiency, defined as creatinine clearance

<50 mL/min. After an intensive lead-in period to monitor for adherence and early drug toxicities, clinical follow-up continues every 3 months. Treatment failure is diagnosed primarily by clinical or immunologic criteria; virologic testing is not widely available.¹²

Patient-level data are routinely entered into the program's electronic medical record,^{13, 14} including detailed information regarding pharmacy refills at each visit. Deaths are recorded in the medical record after confirmation from family members, friends, or community health workers. "Inactive" patients have formally withdrawn from the HIV treatment program. "Late" patients are more than a month overdue for their last scheduled clinical and/or pharmacy visit. Through a clinic-based follow-up program, community health workers trace patients with missed visits.¹⁵

Analysis cohort

We compared the clinical and programmatic outcomes among patients initiating TDF-, ZDV-, and d4T-based ART regimens. We analyzed programmatic data from treatment-naïve adults (> 16 years) initiating ART across 18 primary care sites in Lusaka, Zambia from July 1, 2007 to January 31, 2009. Since the prescription of ART regimens may be based on specific medical conditions (e.g. anemia, renal insufficiency), we recognize the potential for "confounding by indication."¹⁶ Although statistical methods can adjust for measured imbalances between the study groups, the possibility of residual confounding remains. For these reasons, we restricted our analysis to individuals with hemoglobin concentration ≥ 10 g/dL and creatinine clearance ≥ 50 mL/min at baseline – the two primary contraindications to specific ART regimens – in an attempt to minimize this potential bias. To compare demographic and clinical characteristics among individuals initiating different ART regimens, we analyzed categorical variables using Pearson's Chi-square test. Wilcoxon rank-sum tests were used to compare continuous variables. Rates were calculated with 95% exact Poisson confidence intervals (CI).

Clinical and programmatic outcomes

We examined the relative impact of ART regimen on three outcomes: (1) drug substitution of the NRTI of interest (i.e. TDF, ZDV, d4T), a surrogate for drug toxicity; (2) mortality; and (3) "program failure," a composite outcome comprising dead, inactive, and late patients. Owing to the high rates of early mortality noted in our population and others,^{8, 17, 18} we examined ≤ 90 day, > 90 day, and overall outcomes. We fit Kaplan-Meier curves to evaluate crude survival according to drug exposure category. We performed Cox proportional hazards regression to determine the hazard of each of the above-mentioned outcomes and the contribution of key covariates to those estimates. Inactive patients are censored as of the date they withdrew from care and late patients are censored a month after their last scheduled visit.

In primary analysis, we categorized drug exposure for mortality and program failure based on an individual's prescribed ART regimen at the start of the follow-up period, as has been done in previous studies.¹⁹ For our ≤ 90 day and overall analyses, this was based on first prescription. For our post-90 day mortality, drug exposure was based on the regimen the patient was taking at day 90; however, we adjusted for drug substitution in the preceding interval. Baseline factors previously shown to be associated with mortality in our setting⁸ were included in the multivariable analysis: age, sex, body mass index, CD4 count, hemoglobin, World Health Organization (WHO) clinical stage, serum creatinine, and tuberculosis co-infection at enrollment. We included a measure of early adherence in the post-90 day analysis, using a variation of the commonly-reported medication possession ratio (MPR).^{20, 21} We divided the number of days late for pharmacy refills by total days on therapy over the first 90 days, and then subtracted that percentage from 100%.^{12, 22}

Impact of ART regimens on renal function

Because TDF is associated with renal insufficiency,^{23, 24} we evaluated the impact of each drug regimen on creatinine clearance as calculated by the Cockcroft-Gault formula.²⁵ We limited our analysis to those with available data at six and/or 12 months, since routine creatinine screening has not been widely implemented. We calculated the mean change in creatinine clearance for each regimen and compared them with Student's t-test. We also measured the proportion of individuals in each group whose creatinine clearance dropped below 50 mL/min at six and/or 12 months, and compared them using Pearson's Chi-square test. This threshold has clinical significance, since individuals with creatinine clearance below it require TDF dose adjustment or substitution of the drug.²⁶ All analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina), and were approved by the institutional review boards of the University of Zambia (Lusaka, Zambia) and the University of Alabama at Birmingham (Birmingham, Alabama, USA).

RESULTS

Cohort description

From July 1, 2007 to January 31, 2009, 10,485 ART-naïve adults meeting our eligibility criteria were initiated on HIV treatment. Of these, 6,900 (66%) started a TDF-based regimen; 2,446 (23%) started a ZDV-based regimen; and 1,139 (11%) started a d4T-based regimen (Figure 1). The median time of follow-up was 239 days (interquartile range [IQR]: 98, 385), which varied according to drug category: TDF (median 208 days; IQR: 89, 348), ZDV (median 306 days; IQR: 131, 479), and d4T (median 275 days; IQR: 122, 455). This difference in follow-up can be attributed to the gradual roll-out of TDF-based ART into Lusaka clinics after the Ministry of Health's incorporation of TDF into first-line therapy in July 2007 (Figure 2). Comparison groups differed significantly according to various demographic and baseline medical characteristics. When compared to the ZDV- and d4T-based groups, those using TDF were more likely to be male and more likely to have indicators of severe disease at baseline (e.g. low BMI, low CD4 count, higher clinical stage, more frequent tuberculosis co-infection). Adults starting TDF were also more likely to be prescribed EFV rather than NVP, either to allow once-daily ART dosing or to accommodate the use of rifampin in patients requiring tuberculosis co-treatment (Table 1).

Drug substitutions

TDF was associated with fewer drug substitutions (Figure 3A). Overall, the rates were 9.0 per 100 person-years (95%CI = 8.1–9.9) for TDF, 27.0 per 100 person-years (95%CI = 24.6–29.5) for ZDV and 21.5 per 100 person-years (95%CI = 18.4–24.8) for d4T. In the first 90 days, the switch rates were 8.4 per 100 person-years (95%CI = 7.0–9.9) for TDF, compared to 57.7 per 100 person-years (95%CI = 51.3–64.4) for ZDV and 27.3 per 100 person-years (95%CI = 21.1–34.2) for d4T. After 90 days, the switch rates were 9.3 per 100 person-years (95%CI = 8.2–10.5) for TDF, 13.8 per 100 person-years (95%CI = 11.8–16.0) for ZDV and 18.9 per 100 person-years (95%CI = 15.5–22.7) for d4T. In adjusted analysis, the overall hazard of switching from ZDV and d4T persisted when compared to TDF, with the greatest risk observed over the first 90 days (Table 2). Male sex and use of EFV were associated with reduced hazard for drug substitution. No associations were noted with age, CD4 count, hemoglobin, serum creatinine, clinical disease stage, and tuberculosis co-infection at time of ART initiation (Table 3).

Mortality

Overall mortality for the cohort was 6.6 per 100 person-years (95%CI = 6.0–7.2), with considerable higher mortality noted in the first 90 days (13.5 per 100 person-years; 95%CI = 12.1–15.1) than after 90 days (3.3 per 100 person-years; 95%CI = 2.8–3.9; FIGURE 3B). In

multivariable Cox proportional hazards models, overall mortality for those starting TDF were not statistically different from those initiating ZDV (AHR 0.81, 95% CI = 0.62–1.06) or d4T (AHR = 1.03, 95% CI = 0.74–1.43). These trends were consistent in sub-analyses restricted to the first 90 days or after 90 days. Low BMI, low CD4 count, low hemoglobin, and advanced disease stage at baseline were all associated with elevated hazard of mortality. Women had higher risk of death, while individuals on tuberculosis treatment at time of ART initiation had lower risk of death (Table 3).

Programmatic failure

We observed a high rate of programmatic failure within the cohort (31.0 per 100 person-years; 95% CI = 30.0–32.3). The overall rate was 32.2 per 100 person-years (95% CI = 30.5–33.9) for TDF; 28.1 per 100 person-years (95% CI = 25.9–30.5) for ZDV; and 32.2 per 100 person-years (95% CI = 28.5–36.0) for d4T (Figure 3C). In adjusted models, hazards for programmatic failure among the ZDV and d4T groups were not statistically different from that of TDF (Table 2). Factors associated with programmatic failure were similar to those observed for the mortality outcome (Table 3).

Changes in renal function

Overall, 3539 of 6164 (57%) cohort members had creatinine clearance data available within the six-month visit window. This was highest among those initiating TDF (2759 of 3776; 73%), followed by ZDV (523 of 1646; 32%) and d4T (257 of 742; 35%). The mean change between baseline (i.e. ART initiation) and six months was –14.7 mL/min for TDF, –12.7 mL/min for ZDV, and –13.8 mL/min for d4T ($p > 0.05$ for all comparisons). At six months, the proportion of individuals with creatinine clearance < 50 mL/min was 73 of 2759 (2.6%; 95% CI = 2.1–3.3%) for TDF, 5 of 523 (1.0%; 95% CI = 0.3–2.2%) for ZDV, and 6 of 257 (2.3%; 95% CI = 0.9–5.0%) for d4T. The proportion in the TDF group was similar to that of d4T ($p = 0.76$), but higher than that of ZDV ($p = 0.02$).

At 12 months, 1402 of 3023 (46%) cohort members had creatinine clearance information available. Again, this was higher among individuals starting TDF (960 of 1560; 62%) compared to ZDV (294 of 1035; 28%) and d4T (148 of 428; 35%). Mean change between baseline and 12 months were –22.0 mL/min for TDF, –23.7 mL/min for ZDV, and –22.8 mL/min for d4T ($p > 0.05$ for all comparisons). At 12 months, the proportion of individuals with creatinine clearance < 50 mL/min was 30 of 960 (3.1%; 95% CI = 2.1–4.4%) for TDF, 7 of 294 (2.4%; 95% CI = 1.0–4.8%) for ZDV, and 7 of 148 (4.7%; 95% CI = 1.9–9.5%) for d4T had creatinine clearance < 50 mL/min. The proportions for d4T ($p = 0.31$) and ZDV ($p = 0.51$) were not statistically different compared to that of TDF.

DISCUSSION

Our early experience demonstrates that TDF is associated with fewer drug substitutions when compared to ZDV and d4T, a difference most pronounced in the first 90 days following ART initiation. When we compared the drug regimens according to other clinical and programmatic outcomes, no differences were noted. Although these results should be considered preliminary, the overall benefit associated with TDF is encouraging for programs that have incorporated the agent into first-line ART.

Rates for drug substitution for ZDV and d4T were consistent with our previous analysis of the Lusaka cohort.⁸ Most substitutions occurred within the first 90 days, particularly for ZDV. After 90 days, the rates for ZDV and d4T substitutions converged but remained higher than that of TDF. In multivariable Cox proportional hazards models, the risk for drug substitution for ZDV was nearly 7-fold higher than TDF during the 90 first days, but then approximated

that of TDF in the interval that followed. Similar trends were observed for d4T, but significant differences were noted in both periods. These findings are consistent with data from clinical trials of TDF, where the agent was associated with fewer adverse events when compared to either ZDV or d4T.^{1, 2} They also demonstrate the positive impact of TDF in terms of regimen tolerability, a critical characteristic in settings where drug options may be limited.²⁷

TDF has been shown to be an effective component of ART in a number of clinical trials. In separate studies, TDF-based regimens were found to be comparable to d4T-based regimens and superior to ZDV-based regimens in terms of virologic suppression.^{1, 2} Because clinically-evident disease progression is known to lag behind virologic treatment failure, we were not surprised to see the similar survival rates among the three comparison groups during this relatively short follow-up period. There appeared to be a trend towards improved survival associated with ZDV in our overall analysis, but it was not statistically significant. We believe this to be a limitation of our observational database, likely from the high degree of switching within the first 90 days among patients prescribed ZDV. It is also possible that, despite our efforts to control for disease status on our multivariable models, there was residual confounding from the considerably better health status among patients initiating ZDV.

Although many cohorts have focused solely on mortality as an outcome, the high rate of follow-up losses observed in many African programs suggests that ascertainment of vital status may be incomplete.^{15, 28, 29} Even when an “active” system for case finding is employed – as has been done in our setting – reporting of deaths may be delayed or missed altogether.³⁰⁻³² For this reason, we evaluated the outcome of program failure to provide a comprehensive, composite metric by accounting for death, program withdrawals, and follow-up losses. We found that the initial drug regimen was not related to differences in overall program failure. More targeted work is needed to determine whether TDF-based regimens, because of their reduced pill burden, can lead to improved adherence, retention, and virologic outcomes.

Although creatinine clearance data were not available for a significant proportion of cohort members – a noted limitation of this exploratory analysis – our results provide some reassurance regarding the impact of TDF-based ART on renal function at a population level. Unlike what has been observed in other African programs,^{33, 34} mean creatinine clearance appeared to decrease over time across all patients initiating ART, but it is unclear whether these changes are clinically meaningful. Less than 3% of patients initiating TDF had a decline of creatinine clearance to below 50 mL/min, a percentage similar to that of ZDV and d4T at 12 months. This finding is consistent with clinical trials data.^{35, 36} Future work should focus on identifying cost-effective and resource-appropriate algorithms for the monitoring of renal function among patients on long-term TDF. Although the renal failure appears to be a rare complication, it is difficult to detect clinically and may lead to severe long-term sequelae.

To our knowledge, this is the first report of clinical and programmatic outcomes associated with TDF-based ART in sub-Saharan Africa. We were able to reliably capture drug dispensations and link them to medical and outcomes information for a large population of adults on HIV treatment. However, we note several limitations. First, like many observational cohort analyses, there are inherent boundaries to the statistical methods used to draw associations between the drug regimens and clinical outcomes. Patients were allocated to the different comparison groups for reasons that were both selective (e.g. medical contraindications) and random (e.g. drug availability, provider preferences). We attempted to adjust for many of these potential effects through multivariable regression, but acknowledge the possibility of residual confounding. Second, in an effort to minimize “confounding by indication,” we restricted our analysis cohort to individuals without anemia or severe renal insufficiency. Although we believe this approach was effective, it did limit the number of individuals who could contribute person-time in our analysis. Future work should consider

alternative methodologies (e.g. use of propensity scores) to limit such biases without sacrificing sample size. Finally, our inability to reliably measure treatment failure was another limitation of this report. Numerous studies have highlighted the poor performance of immunologic algorithms³⁷⁻³⁹ and the cost of routine virologic monitoring is prohibitive in our setting. For those reasons, we elected to focus on other clinical (e.g. mortality, toxicity) and programmatic (e.g. retention) outcomes for this analysis.

In summary, we observed favorable early outcomes with TDF-based ART. TDF was better tolerated, an important consideration in settings where drug options are limited. No differences were noted among regimens in terms of mortality or program failure. In a limited subset analysis, we found a low prevalence of severe renal insufficiency (i.e. < 50 mL/min) at six and 12 months following ART initiation, with no increased risk associated with TDF use. Although longer term data are clearly needed to fully validate Zambia's policy choice, these findings demonstrate the advantages of TDF-based regimens in African settings and support their continued use in the context of rapid service expansion. They also suggest that the up-front investments in first-line therapy – such as with TDF – may be a cost-effective strategy to increase regimen durability and improve overall patient outcomes.

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Figure 1.
HIV-infected adults initiating antiretroviral therapy across 18 Lusaka primary care sites from July 1, 2007 to January 31, 2009

Figure 2.

Numbers of HIV-infected adults initiated on each of the three primary nucleoside reverse transcriptase inhibitor backbones for antiretroviral therapy from July 1, 2007 to January 31, 2009.

Figure 3.

Kaplan-Meier analysis describing over time drug substitution (A), mortality (B), and “program failure” (C), stratified by initially prescribed nucleoside reverse transcriptase inhibitor backbones for antiretroviral therapy. Program failure comprised mortality, program withdrawals, and follow-up losses.

Comparison of participants according to initially-prescribed nucleoside reverse transcriptase inhibitor backbone for antiretroviral therapy in Lusaka, Zambia (July 1, 2007 to January 31, 2009).

Table 1

	<u>Tenofovir + emtricitabine (N = 6,900)</u>			<u>Zidovudine + lamivudine (N = 2,446)</u>			<u>Stavudine + lamivudine (N = 1,139)</u>		
	N	Value		N	Value		N	Value	P*
Age, median years (IQR)	6,900	35 (30, 41)		2,446	34 (29, 39)		1,139	33 (28, 39)	< 0.01
Male, %	3,373	48.9%		912	37.3%		333	29.2%	< 0.01
BMI, median (IQR)	6,828	20.1 (18.2, 22.2)		2,415	21.1 (18.9, 23.8)		1,127	20.9 (18.8, 23.5)	< 0.01
≥ 16 kg/m ²	6,431	94.2%		2,320	96.1%		1,078	95.7%	0.05
< 16 kg/m ²	397	5.8%		95	3.9%		49	4.3%	
Baseline CD4, median (IQR)	6,845	149 (84, 210)		2,422	171 (105, 228)		1,124	176 (103, 259)	< 0.01
≥ 200	1,986	29.0%		886	36.6%		436	38.8%	< 0.01
≥ 50 to < 200	3,970	58.0%		1,312	54.2%		562	50.0%	
< 50	889	13.0%		224	9.2%		126	11.2%	
Baseline hemoglobin, median (IQR)	6,900	11.8 (10.8, 12.9)		2,446	12.0 (11.2, 13.1)		1,139	11.0 (10.4, 12.3)	< 0.01
≥ 14 g/dL	728	10.6%		295	12.1%		106	9.3%	< 0.01
≥ 12 to < 14 g/dL	2,406	34.9%		994	40.6%		255	22.4%	
≥ 10 to < 12 g/dL	3,766	54.6%		1,157	47.3%		778	68.3%	
Tuberculosis (active)	924	13.4%		201	8.2%		99	8.7%	< 0.01
WHO Stage									
Stage I or II	2,531	37.0%		1,283	52.8%		554	49.6%	< 0.01
Stage III	3,882	56.7%		1,033	42.5%		499	44.6%	
Stage IV	436	6.4%		112	4.6%		65	5.8%	
Serum creatinine, median (IQR)	6,900	66 (54, 79)		2,446	61 (50, 72)		1,139	60 (48, 73)	< 0.01
≥ 120	6,842	99.2%		2,435	99.6%		1,129	99.1%	0.89
< 120	58	0.8%		11	0.4%		10	0.9%	
Third ART drug									
Nevirapine	3,007	43.6%		2,209	90.3%		1,002	88.0%	< 0.01
Efavirenz	3,893	56.4%		237	9.7%		137	12.0%	
Follow-up days, median (IQR)	6,900	208 (89, 348)		2,446	306 (131, 479)		1,139	275 (122, 455)	< 0.01

* Compared to patients initiating tenofovir. BMI = body mass index, WHO = World Health Organization, ART = antiretroviral therapy, IQR = intraquartile range

Table 2

Adjusted hazard ratios (with 95% confidence intervals) for clinical and programmatic outcomes by nucleoside reverse transcriptase inhibitor backbone for antiretroviral therapy in Lusaka, Zambia (July 1, 2007 to January 31, 2009)

	≤ 90 days	> 90 days	Overall
Drug substitution			
TDF + FTC	Ref	Ref	Ref
ZDV + 3TC	6.92 (5.31 - 9.03)	1.08 (0.84 - 1.40)	2.74 (2.30 - 3.28)
d4T + 3TC	2.91 (2.05 - 4.13)	1.34 (1.01 - 1.76)	1.92 (1.55 - 2.38)
Mortality			
TDF + FTC	Ref	Ref	Ref
ZDV + 3TC	0.80 (0.57 - 1.13)	0.67 (0.40 - 1.12)	0.81 (0.62 - 1.06)
d4T + 3TC	0.97 (0.63 - 1.50)	1.18 (0.66 - 2.11)	1.03 (0.74 - 1.43)
Programmatic failure			
TDF + FTC	Ref	Ref	Ref
ZDV + 3TC	1.00 (0.84 - 1.19)	0.96 (0.82 - 1.13)	0.99 (0.88 - 1.11)
d4T + 3TC	1.10 (0.88 - 1.38)	1.21 (0.99 - 1.46)	1.11 (0.96 - 1.28)

All analyses adjusted for age, sex, body mass index, CD4 count, hemoglobin, World Health Organization clinical stage, serum creatinine, tuberculosis co-infection at enrollment, and third antiretroviral agent. Previous drug substitution and adherence also included in the post-90 day analysis. TDF = tenofovir, FTC = emtricitabine, ZDV = zidovudine, d4T = stavudine, 3TC = lamivudine.

Table 3

Patient characteristics associated with overall clinical and programmatic outcomes in Lusaka, Zambia (July 1, 2007 to January 31, 2009).

		Adjusted hazard ratio (95% confidence interval)		
		Drug substitution	Mortality	Programmatic failure
Age	> 15 to ≤ 29 years	Ref	Ref	Ref
	> 30 to ≤ 35 years	0.97 (0.81 - 1.15)	0.86 (0.66 - 1.13)	0.82 (0.73 - 0.92)
	>35 to ≤ 41 years	0.96 (0.80 - 1.16)	0.94 (0.71 - 1.24)	0.80 (0.70 - 0.90)
	> 41 years	0.91 (0.76 - 1.09)	1.05 (0.81 - 1.37)	0.79 (0.70 - 0.88)
Sex	Female	Ref	Ref	Ref
	Male	0.73 (0.63 - 0.85)	1.82 (1.47 - 2.26)	1.43 (1.30 - 1.57)
Body mass index	≥ 16 kg/m ²	Ref	Ref	Ref
	< 16 kg/m ²	1.21 (0.89 - 1.63)	3.09 (2.40 - 3.98)	2.01 (1.72 - 2.35)
CD4 count	≥ 200	Ref	Ref	Ref
	≤ 50 to < 200	0.95 (0.82 - 1.10)	2.03 (1.55 - 2.66)	0.95 (0.86 - 1.05)
	< 50	1.09 (0.88 - 1.36)	3.70 (2.71 - 5.06)	1.27 (1.10 - 1.45)
Hemoglobin	> 14 g/L	Ref	Ref	Ref
	12 to < 14 g/L	0.98 (0.77 - 1.26)	1.30 (0.88 - 1.91)	1.12 (0.96 - 1.31)
	10 to < 12 g/L	1.20 (0.94 - 1.54)	1.68 (1.14 - 2.49)	1.37 (1.17 - 1.60)
Tuberculosis	No	Ref	Ref	Ref
	Yes	0.90 (0.71 - 1.13)	0.64 (0.48 - 0.86)	0.83 (0.72 - 0.95)
WHO stage	I or II	Ref	Ref	Ref
	III	1.08 (0.94 - 1.24)	1.90 (1.49 - 2.44)	1.12 (1.02 - 1.24)
	IV	1.27 (0.96 - 1.66)	2.31 (1.59 - 3.35)	1.19 (0.99 - 1.42)
Serum creatinine	< 120 mmol/L	Ref	Ref	Ref
	≥ 120 mmol/L	0.76 (0.31 - 1.86)	0.60 (0.15 - 2.46)	1.12 (0.63 - 1.99)
Third ART drug	Nevirapine	Ref	Ref	Ref
	Efavirenz	0.69 (0.57 - 0.84)	1.13 (0.89 - 1.43)	1.15 (1.03 - 1.29)

All of the above covariates were included in the Cox proportional hazards model. We also included nucleoside reverse transcriptase inhibitor backbone. WHO = World Health Organization, ART = antiretroviral therapy