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Impact of Baseline Renal Function on Tenofovir-containing Antiretroviral Therapy Outcomes in Zambia

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Summary: In this large cohort of HIV-infected patients on first-line ART in Zambia, individuals who started a tenofovir-containing regimen despite baseline renal dysfunction showed comparable mortality and renal function improvement to those not on tenofovir.

ABSTRACT

***Background*.** Although tenofovir (TDF) use has increased as part of first-line antiretroviral therapy (ART) across sub-Saharan Africa, renal outcomes among patients receiving TDF remain poorly understood. We assessed changes in renal function and mortality in patients starting TDF- or non-TDF-containing ART in Lusaka, Zambia.

***Methods*.** We included patients aged ≥16 years who started ART from 2007 onward, with documented baseline weight and serum creatinine. Renal dysfunction was categorized as mild (eGFR 60-89 mL/min), moderate (30-59 mL/min) or severe (<30 mL/min) using the CKD-EPI formula. Differences in eGFR during ART were analyzed using linear mixed-effect models, the odds of developing moderate or severe eGFR decrease with logistic regression and mortality with competing risk regression.

Results. We included 62,230 adults, of which 38,716 (62%) initiated a TDF-based regimen. The proportion with moderate or severe renal dysfunction at baseline was lower in the TDF compared to the non-TDF group (1.9% vs. 4.0%). Among patients with no or mild renal dysfunction, those on TDF were more likely to develop moderate (adjusted OR: 3.11; 95%CI: 2.52-3.87) or severe eGFR decrease (adjusted OR: 2.43; 95%CI: 1.80-3.28), although the incidence of such episodes was low. Among patients with moderate or severe renal dysfunction at baseline, renal function improved independently of ART regimen and mortality was similar in both treatment groups.

Conclusions. TDF use did not attenuate renal function recovery or increase mortality in patients with renal dysfunction. Further studies are needed to determine the role of routine renal function monitoring before and during ART use in Africa.

INTRODUCTION

In 2007, Zambia was one of the first countries in sub-Saharan Africa (SSA) to introduce Tenofovir Disoproxil Fumarate (TDF) as a preferred nucleotide reverse transcriptase inhibitor (NRTI) of first line antiretroviral therapy (ART) [1, 2]. The advantages of TDF include its high potency against HIV and hepatitis B infections, favorable resistance profile, good tolerability and safety, and its availability as a co-formulation with other antiretroviral agents in once-daily pills [3-5]. However, in industrialized countries, TDF has been associated with nephrotoxicity, including proximal tubulopathy and impaired glomerular filtration [6-11]. In SSA, a significant number of HIV-infected patients start ART with pre-existing kidney dysfunction, due to either HIV-associated nephropathy or to other causes such as hypertension or diabetes [12, 13]. Although the incidence of TDF-related kidney dysfunction appears to be low in most settings [8-10, 14], the impact of TDF on clinical outcomes in patients starting ART with moderate or severe renal dysfunction has not been studied previously. In this report, we evaluated changes in renal function and mortality in patients starting TDF- or non-TDF-containing ART regimens in a large cohort of HIV infected adults in Lusaka, Zambia.

METHODS

The Zambian National HIV Program

Care and treatment provided through the Zambian National HIV Program has been described previously [15]. Alongside a detailed medical history and physical examination, the baseline screening includes CD4 cell count, hemoglobin, serum

creatinine, and aminotransferases. The choice of ART depends on laboratory test results, age and comorbidities. Before June 2007, stavudine (d4T) or zidovudine (AZT) with 3TC plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), either nevirapine (NVP) or EFV, were the recommended first-line agents. Thereafter, TDF replaced d4T and AZT as the preferred NRTI alongside 3TC for patients with a creatinine clearance ≥ 50mL/minute. However, as creatinine clearance was not calculated routinely, TDF was prescribed in patients with a serum creatinine ≤ 120 µmol/L. For those with impaired renal function, abacavir (ABC) was prescribed instead of TDF. Routine clinical follow-up visits were done every 3 to 6 months and TDF was substituted with ABC in patients who developed severe renal dysfunction. Deaths are ascertained when reported by a family member, clinic staff member, or community health worker. Patient medical information is entered into an electronic database for clinical care, monitoring and evaluation, and reporting purposes [16]. These programmatic data have received local ethical approval for use in the International epidemiological Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) network, a large regional collaboration of ART programmes [17].

Inclusion criteria, definitions, and outcomes

We included patients aged ≥16 years who started ART in the capital city of Lusaka from June 2007, when the Zambian government instituted its national policy to incorporate TDF into first-line ART [1]. Those without documented serum creatinine and weight at baseline were excluded from the analysis cohort. Due to a lag in roll out of national ART guidelines, not all the patients enrolled after June 2007 initiated a TDF-containing ART

regimen. We categorized first-line regimens as either TDF-containing regimens (TDF + XTC [3TC or FTC] + NVP or EFV) or non-TDF-containing regimens (ABC or d4T or AZT + 3TC + NVP or EFV). Although boosted protease inhibitors (bPI) may be incorporated into first-line regimens following NNRTI intolerance, they are typically reserved for second-line therapy and are almost never prescribed at ART initiation. In addition, because the co-administration of TDF with a bPI has been shown to increase the risk of nephrotoxicity and impair renal function [18-20], we excluded all patients who were on a bPI-based regimen. As ABC was often prescribed to patients with renal dysfunction at baseline, including these patients could have introduced some degree of confounding by indication. In an effort to minimize this potential effect, we conducted secondary analyses that excluded patients on ABC.

Serum creatinine concentration was measured using the Cobas Integra 400 Plus automated chemistry analyzer (Roche Diagnostics, Basel, Switzerland) from 2007-2008, and the Olympus AU400 analyzer (Beckman Coulter Diagnostics, Brea, California, USA) thereafter. Quality control of chemistry analyzers was performed according to manufacturer recommendations. We estimated the glomerular filtration rate (eGFR) using the CKD- Epidemiology (CKD-EPI) formula [21]. This method is considered more accurate than the Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) equations for values > 60 mL/min/1.73 m^2 and has recently been shown to be accurate in HIV-infected populations as well [22]. In sensitivity analyses, we repeated the main analyses using the MDRD and the Cockroft-Gault formulas. In line with the Kidney Disease Outcomes Quality Initiative (KDOQI) criteria [23, 24], we categorized renal function as follows: normal: eGFR ≥90 mL/min/1.73m^2, mild eGFR

decrease: eGFR 60 - 89 mL/min/1.73m^2, moderate eGFR decrease: eGFR 30 - 59 mL/min/1.73m^2) and severe eGFR decrease: eGFR ≤29 mL/min/1.73m^2. Our outcomes of interest were: 1) renal function after 6 and 12 months of ART, 2) the proportion of patients developing an episode of moderate or severe eGFR decrease while on ART, and 3) mortality.

Statistical analyses

Baseline characteristics of patients initiating TDF- and non-TDF-containing ART were compared using Chi-squared and Mann–Whitney tests. We compared the median change in eGFR between patients on TDF and those not on TDF after 6 and 12 months of ART, according to baseline renal function category. To estimate the difference in renal function over time between the two study groups, we used a multivariable mixed-effects model (eGFR measurements within patients), using a random intercept with unstructured covariance correlation structure, stratified by baseline renal dysfunction category. The proportion of patients with a normal renal function or mild renal dysfunction at baseline who developed an episode of moderate or severe eGFR decrease at 6 or 12 months was compared between the TDF and non TDF groups. Adjusted estimates were obtained using a multivariable logistic regression model. We used a multivariable competing risk sub-distribution model according to Fine and Gray to compare mortality between the two groups, measuring time from the initiation of first-line ART to the outcome of interest [25]. Accounting for loss to follow-up (LTFU), defined as not returning to the health care facility for more than six months, as a competing risk of death, limits the production of biased results. All multivariable

regression analyses were adjusted for age, sex, calendar year, WHO stage, CD4 count, and hemoglobin. Anemia was defined as severe (hemoglobin <5.0 mmol/L (<8.0 g/dL)), moderate (5.0–<6.2 mmol/L (8.0-<10.0 g/dL) in women and 5.0–<6.8 mmol/L (8.0-<11.0 g/dL)in men), mild (6.2–<7.4 mmol/L (10.0-<12.0 g/dL) in women and 6.8–<8.1 mmol/L (11.0-<13.0 g/dL) in men) or none (≥7.4 mmol/L (≥12.0 g/dL) in women and ≥8.1 mmol/L (≥13.0 g/dL) in men). All statistical analyses were performed using Stata software version 12.1 (College Station, TX).

RESULTS

Baseline Characteristics

In this analysis, we included 62,230 HIV-infected adults who initiated ART between January 2007 and February 2011. Of these, 38,716 (62%) started a TDF-containing first-line regimen (Table 1). Individuals on TDF started ART with a more advanced stage of disease and were more likely to receive EFV compared to those not on TDF. Patients not on TDF-containing regimens were more likely to be female and to have started ART in earlier years. Age and hemoglobin were similar across treatment groups. Overall, patients on TDF were slightly more likely to have some degree of baseline renal dysfunction compared to individuals not on TDF-containing ART (16.7% vs. 12.4%). However, the proportion of patients with moderate or severe renal dysfunction was two times higher in the non-TDF compared to the TDF group (4.0% vs. 1.9%). After ART initiation 70.4% of patients on TDF and 84.9% of those on non-TDF regimens had at least one repeat creatinine measurement available at either 6 or 12 months of ART.

Changes in renal function in patients with no or mild eGFR decrease at baseline

Among patients who started ART with no renal dysfunction, we observed a slight decline in renal function both at 6 and 12 months irrespective of ART regimen (-15 ml/min in the TDF and -17 ml/min in the non-TDF groups). There was no change in renal function over time in those with mild eGFR decrease at baseline (Figure 1). In adjusted analyses, patients on TDF had a slightly reduced renal function at 6 and 12 months compared to those on other ART regimens, although differences were small (Table 2). The proportion of patients with no or mild baseline renal dysfunction developing an incident episode of severe eGFR decrease at 6 or 12 months was higher in the TDF group though not statistically significant (0.28% vs. 0.20%; p=0.26 at 6 months and 0.24% vs. 0.15%, p=0.20 at 12 months). For the outcome defined as incident episodes of moderate or severe eGFR decrease, the differences reached statistically significance; however the numbers remained low (1.90% in TDF vs. 1.27% in non-TDF; p<0.001 at 6 months and 1.84% vs. 1.37% p=0.02 at 12 months, Figure 2). In adjusted analyses, patients on TDF were more likely to develop an episode of moderate or severe renal dysfunction compared to those on other regimens during the first year of ART (Table 2).

Changes in renal function in patients with moderate or severe renal eGFR decrease at baseline

Independent of treatment regimen, individuals with moderate (n=616) or severe (n=110) renal dysfunction at baseline showed an improvement in renal function during ART. This

included patents who received TDF despite severe renal failure (+30 mL/min after 12 months, Figure 1). In adjusted analyses, TDF was associated with marginally lower renal function at 1 year in individuals with baseline moderate renal dysfunction. On the contrary, among patients with available data, TDF use seemed to be associated with a higher eGFR during follow-up for those with severe renal dysfunction at ART initiation (adjusted difference: +21.7 mL/min, 95% CI: 4.33-39.10 at 1 year; Table 2). Finally, the odds of progression from moderate to severe dysfunction were not increased for patients starting a TDF-containing ART regimen (aOR 1.11, 95% CI: 0.46, 2.70) (Table 2).

Mortality

Over a total follow-up of 111,972 person-years, 2,405 (6.2%) deaths in the TDF group and 1,472 (6.3%) in the non-TDF patients were documented. 27.4% and 20.7% of patients were LTFU in each group, respectively. Overall, the degree of renal dysfunction at ART initiation predicted mortality. For instance, patients with severe renal dysfunction at baseline were twice as likely to die during follow-up as those with a normal renal function (Table 3). In adjusted analyses stratified by baseline renal function, individuals who started a TDF-containing regimen with some degree of renal dysfunction were not more likely to die during follow-up compared to those on other treatment regimens (Table 2). Notably, there was no detectable difference in mortality between patients on TDF and those not on TDF starting ART with moderate (a-sHR: 0.79, 95% CI 0.58, 1.07) or severe (a-sHR 0.89, 95% CI 0.52, 1.52) eGFR decrease. Other important risk

factors for death were male sex, advanced clinical stage of disease, low CD4 cell counts and anemia (Table 3).

Sensitivity analyses

(1) When the analyses were repeated using the MDRD and Cockcroft-Gault equations to measure eGFR, we found similar results for all the baseline renal eGFR categories (Web-Tables 1A and 1B). Independently of the formula used, mortality and eGFR decrease during follow-up of patients on TDF despite moderate or severe baseline eGFR decrease were not higher compared to the outcomes in patients on other regimens. (2) Of the patients in the non-TDF group, 1,787 patients (7.6%) initiated ABC. Excluding these patients from our analyses did not alter our results significantly (Web-Table 2).

DISCUSSION

In this large observational cohort of HIV-1 infected adults in Zambia, TDF did not have a significant impact on renal function changes or mortality in patients initiating ART with moderate or severe renal dysfunction. Among individuals with no or mild eGFR decrease at baseline, those on TDF were more likely to experience an episode of moderate or severe renal dysfunction within the first 12 months of ART compared to patients on other regimens; however, the overall occurrence of this outcome was rare.

Fifteen percent of the patients included in our study had some degree of renal dysfunction at ART initiation. This is lower than the proportion reported in other studies from sub-Saharan Africa [12, 13]. These differences might have been driven by the degree of immunosuppression at ART start, which was less advanced in our study compared with the two other reports. Recent improvements in screening for co-infections associated with renal dysfunction, the avoidance of nephrotoxic drugs, as well as the change in CD4 threshold for ART initiation are additional factors that could explain this finding. The use of TDF is not recommended for patients with moderate or severe eGFR decrease according to most international guidelines. The Zambian national guidelines state that patients should initiate a TDF-containing regimen only if their creatinine clearance >50mL/min or the absolute serum creatinine ≤ 120 µmol/L. Many clinicians use the absolute creatinine value to determine the ART regimen for reasons of convenience. As a result, TDF is sometimes prescribed to patients with an absolute creatinine ≤ 120 µmol/L but undiagnosed moderate or severe renal eGFR decrease, as was the case for 726 patients receiving TDF (1.9%) in our analysis cohort.

Our study showed that kidney function in individuals with severe baseline eGFR decrease improved during the first year of ART, a finding that was even more pronounced in those receiving TDF. Although the causes of renal dysfunction in patients starting ART in SSA have not been thoroughly investigated, it is assumed that HIV associated nephropathy (HIVAN) plays an important role in this setting [26]. As a consequence, even ART regimens containing potentially nephrotoxic agents can improve renal function in most of the patients with renal insufficiency. Similar to our findings, in a large cohort of American HIV-infected veterans, pre-existing renal disease

did not appear to worsen the effects of TDF [9]. Of the 3,336 DART trial patients included in the analysis of renal outcomes, only 237 (7.0%) had moderate and 7 (0.2%) severe renal dysfunction at ART initiation [12, 14]; however, a detailed analysis of renal change by ART regimen was not performed for these patients [14]. In contrast, our patients who started a TDF-containing regimen with a moderate eGFR decrease were not more likely to develop severe renal dysfunction during ART compared to those on other regimens. As expected, mortality increased with worsening baseline eGFR decrease at baseline. However, TDF was not associated with higher mortality in patients with moderate or severe renal dysfunction at baseline. Taken together, these findings suggest that starting a TDF-containing regimen despite pre-existing renal disease may be less harmful than previously thought.

In our study, patients who started ART with normal kidney function seemed to experience a slow decline of renal function during the first year, irrespective of ART regimen. It has been shown that even though ART seems to slow decline in creatinine clearance, a degree of renal function loss appears inevitable, even with durable viral suppression [27]. Therefore, ART may only improve kidney function if it is HIV or hepatitis B related. In line with recent publications from high-income countries which linked TDF with acute and chronic kidney dysfunction [8-10, 14], individuals on TDF in our analysis experienced more pronounced reductions in renal function compared to those on non-TDF regimens. Furthermore, we observed a two-fold increase in incident moderate or severe eGFR decreases in the TDF group. However, the numbers remained small, with less than 1% of patients experiencing an episode of severe renal

dysfunction (eGFR<30ml/min) 6 or 12 months after ART start. Our findings show that the overall impact of TDF on renal outcomes in patients with normal baseline renal function is small. Considering the low magnitude or even the absence of this association in many previous reports [27, 28] and given its many advantages, poor access to renal function monitoring may not be a good justification for withholding TDF in first-line ART.

To our knowledge, this is the largest study assessing the association between TDF and renal dysfunction in SSA to date. We provide evidence on the safety of TDF-containing regimens in a non-selected population with highly prevalent kidney dysfunction. Whereas many studies have examined renal safety of TDF in patients with normal baseline renal function, ours provides a detailed description of renal outcomes and mortality in patients having received TDF despite pre-existing eGFR decrease. Our main limitation was the significant proportion of patients who did not have a follow-up creatinine measurement (24.1%). Although we cannot exclude the non-random selection of patients who had one or several measurements performed, it is important to note that a significant proportion of individuals on TDF were also missing creatinine measurements, which reflects the situation of most ART programs in southern Africa. Although it is common practice to report renal outcomes as chronic kidney disease (CKD), defined as two eGFR measurements below 60 ml/min at least three months apart, such diagnoses may be difficult in resource-constrained settings such as Zambia, where follow-up testing is not always routinely performed. For this reason, we were unable to further distinguish between acute and chronic renal conditions. As single drug substitutions were not considered in our analyses, a fraction of the patients who

developed renal dysfunction on TDF might have been switched to a non-TDF-containing regimen, which might have had an impact on our mortality and severe eGFR decrease estimates. Some level of confounding by treatment allocation was also possible, as the patients included in this study were not randomized to receive either TDF or non-TDF regimens. Therefore, we adjusted our analyses for differences in baseline demographic and clinical characteristics. Finally, we could not evaluate long-term renal outcomes, and, as creatinine was the only routine measurement of renal function performed in this cohort, we could not assess the mechanisms of renal disease such as proximal tubulopathy, which has been associated with the use of TDF [29].

In summary, in our analysis of a large observational cohort in Zambia, we show that patients receiving TDF-containing ART, despite pre-existing renal disease, did not experience worse renal outcomes or increased mortality compared to those taking other regimens. Baseline screening of renal dysfunction should be encouraged, as dose adjustment of several antiretroviral agents is recommended in case of eGFR decrease. However, our data support the view that, poor availability of renal function screening should not stop the prescription of TDF-containing ART, considering its numerous advantages over other combinations. Studies monitoring and evaluating the long term effect of TDF in HIV-infected population in SSA are urgently needed.

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Potential conflicts of interests. We declare no competing interests.

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Table 1: Baseline Characteristics of study population by ART regimen

	With TDF	Without TDF	p-value
	N=38,716 (62%)	N=23,514 (38%)	
Female (%)	21,891 (56.5)	16,542 (70.4)	<0.001
Median age in years (IQR)	34 (29-40)	32 (27-38)	<0.001
WHO stage III/IV (%)	22,989 (60.2)	11,218 (48.4)	<0.001
Median BMI in kg/m2 (IQR)	19.7 (17.8-22.1)	20.8 (18.5-22.6)	<0.001
Median CD4 cells/µL (IQR)	151 (82-223)	172 (98-251)	<0.001
missing (%)	2,333 (6.0)	1,858 (7.9)	
Anemia (%)			<0.001
None	10,050 (27.9)	5,650 (26.5)	
Mild	13,291 (36.8)	8,486 (39.8)	
Moderate	9,709 (26.9)	5,429 (25.5)	
Severe	3,034 (8.4)	1,760 (8.3)	
missing (%)	2,632 (6.8)	2,189 (9.3)	
eGFR decrease (%)			<0.001
None	32,247 (83.3)	20,621(87.7)	
Mild	5,741 (14.8)	1,967 (8.4)	
Moderate	616 (1.6)	676 (2.9)	
Severe	110 (0.3)	246 (1.1)	
Calendar year of ART start (%)			<0.001
2007	3,204 (8.28)	10,842 (46.1)	
2008	10,155 (26.2)	4,589 (19.5)	
2009	12,319 (31.8)	4,594 (19.5)	
2010	12,110 (31.3)	3,297 (14.0)	
2011	928 (2.4)	192 (0.9)	
EFV-based ART (%)	23,367 (60.4)	3,913 (16.6)	<0.001

TDF: tenofovir; WHO: World Health Organization; BMI: body mass index; ART: antiretroviral therapy; EFV: efavirenz

Table 2: Comparison of renal outcomes and mortality between patients starting ART with and without TDF using CKD EPI (Reference group: patients not on TDF)

Baseline eGFR decrease	Difference in eGFR (ml/min)		Progression to renal dysfunction		Mortality
	At 6 months (95% CI)	At 12 months (95% CI)	Severe OR (95% CI)	Moderate/severe OR (95% CI)	sHR (95% CI)
None	-8.64 (-9.40, -7.88)	-9.93 (-10.7, -9.14)	3.09 (1.85,5.17)	3.11 (2.52, 3.87)	1.22 (1.13, 1.31)
Mild	-4.55 (-6.42, -2.68)	-6.81 (-9.01, -4.61)	5.27 (1.19, 23.2)	2.43 (1.80, 3.28)	0.82 (0.68, 0.98)
Moderate	-6.10 (-11.0, -1.23)	-5.37 (-10.9, 0.14)	1.11 (0.46, 2.70)	N/A	0.79 (0.58, 1.07)
Severe	19.3 (2.29, 36.20)	21.7 (4.33, 39.10)	N/A	N/A	0.89 (0.52, 1.52)

TDF: tenofovir; eGFR: estimated glomerular filtration rate; OR: odds ratio; sHR: sub-hazard ration; 95% CI: 95% confidence interval

All analyses are adjusted for age, sex, calendar year, baseline WHO stage, CD4 cell count and anemia

Table 3: Risk factors of mortality

Factors	Crude SHR (95% CI)	p-value	Adjusted SHR (95% CI)	p-value
TDF		<0.001		0.001
No	1		1	
Yes	1.13 (1.06, 1.21)	<0.001	1.14 (1.05, 1.23)	<0.001
Baseline eGFR decrease				
None	1		1	
Mild	1.19 (1.09, 1.31)		1.24 (1.12, 1.37)	
Moderate	2.52 (2.16, 2.94)		1.80 (1.53, 2.13)	
Severe	3.77 (2.96, 4.80)		2.00 (1.52, 2.63)	
Baseline CD4 count (cells/µL)		<0.001		<0.001
<50	1		1	
50-199	0.46 (0.42, 0.51)		0.60 (0.56, 0.65)	
>199	0.23 (0.20, 0.26)		0.42 (0.38, 0.47)	
Anemia		<0.001		<0.001
None	1		1	
Mild	2.06(1.78, 2.39)		1.63 (1.45, 1.83)	
Moderate	3.82 (3.32, 4.40)		2.70 (2.41, 3.03)	
Severe	5.93 (1.78, 2.39)		3.88 (3.40, 4.43)	
Age (years)	1.01 (1.00, 1.01)	<0.001	1.01 (1.01, 1.01)	<0.001
Sex		<0.001		<0.001
Male	1		1	
Female	0.81 (0.75, 0.88)		0.77 (0.72, 0.83)	
WHO Stage		<0.001		<0.001
Stage I or II	1		1	
Stage III	2.34 (2.13, 2.58)		1.77 (1.62, 1.93)	
Stage IV	2.56 (2.21, 2.97)		2.12 (1.86, 2.41)	
Calendar year at ART start		<0.001		<0.001
2007	1		1	
2008	0.90 (0.80, 1.02)		0.94 (0.86, 1.02)	
2009	0.76 (0.67, 0.85)		0.71 (0.64, 0.78)	
2010	0.30 (0.26, 0.34)		0.49 (0.43, 0.55)	

TDF: tenofovir; WHO: World Health Organization; ART: antiretroviral therapy; sHR: sub-hazard ratio; 95% CI: 95% confidence interval

Figure Legends

Figure 1: Crude change in renal function during ART, by baseline renal function and treatment group

Figure 2. Proportion of patients with no or mild renal dysfunction at baseline developing a moderate or severe eGFR decrease on ART