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Relationship between Renal Dysfunction, Nephrotoxicity and Death among HIV Adults on Tenofovir

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Abstract

Objective—In April 2010 the South African government added Tenofovir disoproxil fumarate to its first-line antiretroviral therapy (ART) for HIV patients. We analyzed the relationship between renal dysfunction at tenofovir initiation, nephrotoxicity and mortality.

Design—Retrospective cohort analysis of HIV-infected adults who received tenofovir and had a creatinine clearance done at initiation at the Themba Lethu Clinic, Johannesburg, South Africa between April 2004–September 2009.

Methods—We estimated the relationship between renal dysfunction, nephrotoxicity [any decline in kidney function from baseline (acute or chronic) that is secondary to a toxin (including drugs)] and mortality for patients initiated on tenofovir-containing regimens using marginal structural models and inverse probability of treatment weights to correct estimates for lost to follow-up and confounding.

Results—Of 890 patients initiated on tenofovir, 573 (64.4%) had normal renal function (>90ml/min), 271 (30.4%) had mild renal dysfunction (60–89ml/min) and 46 (5.2%) had moderate renal dysfunction (30–59ml/min). 2.4% experienced nephrotoxicity, 7.8% died and 9.7% were lost during 48-months of follow-up. Patients with mild (HR 4.8; 95%CI: 1.5–15.2) or moderate (HR 15.0; 95%CI: 3.4–66.5) renal dysfunction were at greatest risk of nephrotoxicity, while those with mild (HR 1.2; 95%CI: 0.7–2.3) or moderate (HR 3.2; 95%CI: 1.3–7.8) renal dysfunction vs. normal renal function were at highest risk of death by 48-months.

Conclusion—Much of the incident renal dysfunction in tenofovir patients is likely related to pre-existing renal pathology, which may be exacerbated by tenofovir. With expanded use of

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tenofovir, screening for renal dysfunction prior to initiation and dose adjustment is necessary to help improve ART outcomes.

Keywords

nephrotoxicity; mortality; lost to follow-up; tenofovir; creatinine clearance; resource-limited setting

INTRODUCTION

It is well known that individuals of African descent are at increased risk of renal failure[1]. Chronic kidney disease is three to four times more frequent in Africa than in industrialized countries in non-HIV patients[2] and nephrotoxicity has been shown to be an important complication of HIV infection, particularly in patients with pre-existing renal dysfunction[3-7]. It may also be induced by the antiretroviral (ARV) drug tenofovir disoproxil fumarate[4, 8, 9]. The prevalence of chronic kidney disease is high (6%) in South African HIV patients[10] and estimates show that 10% (650,000) of patients will suffer from HIV-related renal failure or renal toxicities throughout the course of their disease[11, 12]. As South Africa has recently introduced tenofovir as first-line treatment[13], accurately measuring the prevalence of renal impairment at ART initiation takes on additional importance as patients with pre-existing renal dysfunction may require alternative treatments and intensive monitoring due to a greater risk of renal failure and renal toxicities[14-16].

Tenofovir is eliminated from the kidneys by glomerular filtration and active proximal tubular secretion, which help to maintain metabolic balance (e.g., stable pH) as the kidneys filter the blood. Tenofovir can accumulate in the proximal renal tubular cells[4, 5, 17], resulting in renal toxicity, renal tubular acidosis and, ultimately, renal failure[5, 7], characterized by a decline in glomerular filtration rates (GFR) and hypophosphatemia[18-23].

There is little knowledge regarding the effect of renal impairment on treatment outcomes in patients initiating tenofovir in resource-limited settings[14, 24]. Some studies show low rates of tenofovir-associated renal failure and nephrotoxicity (decline in kidney function from baseline (acute or chronic) that is secondary to a toxin (including drugs))[3, 4, 16, 17, 21], while others suggest a higher risk[4, 19, 21, 22, 24] amongst patients with renal impairment at initiation of tenofovir compared to those with normal renal function. We estimated the relationship between renal dysfunction, nephrotoxicity and mortality for patients initiated on tenofovir-containing regimens using marginal structural models and inverse probability of treatment weights to correct estimates for lost to follow-up (LTFU) and confounding in the Themba Lethu Clinic (TLC), Johannesburg, South Africa.

METHODS

Cohort Description

TLC is a large government HIV treatment site in Johannesburg, South Africa, which has initiated nearly 17,500 patients onto antiretroviral therapy (ART). Care at TLC is provided according to South African National Department of Health guidelines[13].

Use of TLC data was approved by the Human Research Ethics Committee of the University of the Witwatersrand. Approval for analysis of de-identified data was granted by the Institutional Review Board of Boston University.

Eligibility Criteria

Participants were HIV-positive patients seen at TLC, 18 years of age, and either newly initiated or switched onto an ART regimen containing 300mg of tenofovir daily between April 2004-September 2009. They had a creatinine clearance done 6-months prior to two weeks following tenofovir initiation. Patient data was extracted from an electronic patient record system(TherapyEdge-HIV™).

Study variables

We compared ART outcomes (nephrotoxicity and mortality) by 48-months of follow-up stratified by renal function at tenofovir initiation. Nephrotoxicity was defined as any decline in kidney function from baseline (acute or chronic) that is secondary to a toxin (including drugs) and documented by a clinician, within 48-months after initiation onto tenofovir. Mortality is ascertained via South African National Vital Registration Infrastructure Initiative for patients who are LTFU[27-29]. LTFU was defined as having not attended the clinic in 4-months. Creatinine clearance was calculated using the Cockcroft-Gault equation, which estimates creatinine clearance on the basis of the serum creatinine, weight and gender[25]. This surrogate measure of GFR has been validated in sub-Saharan Africa[23]. Creatinine clearance was categorized according to the U.S. National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) as normal (≥ 90 ml/min), mild (60-89ml/min), moderate (30-59ml/min) and severe (<30 ml/min) renal dysfunction[26]. There were no patients in our analysis with severe renal dysfunction at baseline. All but three patients had creatinine clearance levels above 40 ml/min., a level previously reported to not be associated with adverse renal outcomes[42]. If a patient had severe renal dysfunction at baseline, clinician's at Themba Lethu would not initiate them onto tenofovir. The three patients that were initiated below 40 ml/min. were monitored properly by dose adjustment of tenofovir and then switched to a different ARV drug if necessary when renal function worsened.

For nephrotoxicity, person-time accrued from ART initiation until the earliest of: 1) nephrotoxicity; 2) death; 3) LTFU 4) close of the dataset (01 September 2010). For death, person-time accrued from ART initiation until the earliest of: 1) death; 2) LTFU; or 3) close of the dataset (01 September 2010). Patients who transferred were censored at their last clinic visit.

Statistical analysis

Patient characteristics and outcomes were stratified by renal function at tenofovir initiation and summarized as simple proportions. Marginal structural modelling using inverse probability of treatment weights were used to adjust for confounding and selection bias due to LTFU[30-32]. Marginal structural models are a class of regression models which attempt to create a pseudo-population in which confounding and LTFU are not present by weighting subjects rather than including covariates in the regression model. Stabilized weights were obtained by fitting two pooled logistic regression models; one controlling for baseline predictors of LTFU (creatinine clearance level, time on ART, WHO stage III/IV, gender, age, CD4 count, Body Mass Index (BMI) and haemoglobin) and a second model controlling for baseline predictors in addition to current predictors (current CD4 count, current BMI, current haemoglobin and current viral load status) of becoming lost. We estimated the parameters of our marginal structural Cox model by calculating a stabilized weight for each person-month and fitting a weighted pooled logistic model controlling for baseline covariates and current viral load (<400 or ≥ 400 copies/mL) to estimate predictors of death and nephrotoxicity.

RESULTS

A total of 1,322 patients received a tenofovir-containing regimen at TLC from April 2004-September 2009. We excluded 432 patients who had no creatinine clearance at initiation. The 432 patients excluded were similar in demographic and clinical characteristics at tenofovir initiation to those included, except they had a slightly lower median CD4 count (200 cells/mm³; IQR 97-330). The remaining 890 patients had a median age of 37.1 years (IQR 32.5-43.4), median CD4 count of 245 cells/mm³ (IQR 115-426), were predominately black (96.3%), female (73.5%) and were on tenofovir for a median of 10.8 months (IQR 6.5-16.6)(Table 1). A total of 573 (64.4%) patients had normal levels of renal function (>90ml/min), 271 (30.5%) had mild (60-89ml/min) renal dysfunction and 46 (5.2%) had moderate (30-59ml/min) renal dysfunction at tenofovir initiation.

A total of 190 patients were ART-naïve at tenofovir initiation, while 700 were switched onto tenofovir. Among the 700 patients switched, over 45% did not have a reason for switching listed; for those that did the most common reasons were d4T toxicity (48.4%), severe anemia (3.6%) and virologic failure (2.4%). Patients with below normal renal function at tenofovir initiation were older and were more likely to present with WHO stage III/IV, a lower median CD4 count, lower haemoglobin and lower BMI at initiation compared to those with normal renal function(Table 1). Patients who had moderate renal dysfunction at initiation of tenofovir had a shorter time on tenofovir (7.5 months; IQR 1.8-16.7) than those with normal (10.9 months; IQR 6.9-16.8) or mild (10.9 months; IQR 5.6-16.0) dysfunction.

48-Month Outcomes

Among 890 patients, 21 (2.4%) experienced nephrotoxicity, 69 (7.8%) died and 86 (9.7%) were LTFU during 48-months of follow-up(Table 1). Median follow-up time for patients who experienced nephrotoxicity, or died was 3.6 months (IQR 1.0-12.5) and 2.6 months (IQR 0.9-5.3), respectively. Rates of nephrotoxicity (normal-0.4/100 pys, mild-2.5/100 pys and moderate-10.7/100 pys) and death (normal-3.0/100 pys, mild-5.5/100 pys and moderate-21.9/100 pys) increased with decreasing renal function(Table 2). Of the 21 patients that developed nephrotoxicity none were LTFU, however six went on to die within 2.3 months (IQR 2.2-2.5) after diagnosis. When stratified by baseline creatinine clearance level, one patient with normal renal function died within 2.2 months (IQR 2.2-2.2), while three with mild renal dysfunction died within 2.5 months (IQR 2.3-7.3) and two with moderate renal dysfunction died within 2.1 months (IQR 1.9-2.3) of being diagnosed with nephrotoxicity.

Nephrotoxicity

In adjusted models the strongest risk factor for nephrotoxicity was having mild (HR 4.8; 95%CI: 1.5-15.2) or moderate (HR 15.0; 95%CI: 3.4-66.5) renal dysfunction compared to patients with normal renal function (Table 2). Patients 40 years of age, those with low haemoglobin, patients with a low CD4 count and those with a current detectable viral load were also at increased risk of nephrotoxicity. Additionally, we stratified our analysis by treatment status (naïve or switched) at tenofovir initiation. Although the estimates lacked precision when stratified, we found that among those who were switched onto tenofovir, patients with a mild (HR 5.3; 95%CI 1.4-19.8) or moderate (HR 24.5; 95%CI 3.2-188.2) renal dysfunction appeared at higher risk of nephrotoxicity compared to patients naïve at tenofovir initiation (mild-HR 4.4; 95%CI 0.4-45.8, moderate-HR 14.3; 95%CI 1.4-149.5).

Mortality

Patients with mild (HR 1.2; 95%CI: 0.7-2.3) or moderate (HR 3.2; 95%CI: 1.3-7.8) renal dysfunction were at greatest risk of death during follow-up vs. patients with normal renal

function. Male patients, those with lower CD4 count, those with low haemoglobin and patients with low BMI at tenofovir initiation were also at increased risk of mortality. When stratified by treatment status (naïve or switched) at tenofovir initiation we again found variation in the estimates. Patients who were switched onto tenofovir and had a moderate renal dysfunction were at higher risk (HR 5.2; 95% CI 1.6-17.0) of death compared to patients naïve at tenofovir initiation also with moderate renal dysfunction (HR 1.6; 95% CI 0.4-6.6).

DISCUSSION

As a result of limited use of tenofovir in resource-limited settings, this is one of the first studies to examine the relationship between renal dysfunction at tenofovir initiation, diagnosis of nephrotoxicity and mortality. The frequency of nephrotoxicity in this cohort (2.4%) is similar to that reported in other studies[33-36]. As expected, the risk of nephrotoxicity and death by 48-months of follow-up increased with decreasing renal function at initiation of tenofovir. Additionally, patients switched onto tenofovir had a higher risk of nephrotoxicity and death compared to ART-naïve patients. However, unlike previous literature we did not find that females were at higher risk of developing nephrotoxicity than males in this cohort[3, 9, 37]. Additionally, because our cohort is 96.3% black we were not able to determine potential differences in risk of clinical outcomes between races as previously reported[38].

Research has shown that the APOL1 risk alleles, found on chromosome 22, were present in more than 30% of individuals of African descent with focal segmental glomerulosclerosis, the glomerular lesion of HIV-associated nephropathy[39]. A recent renal biopsy study confirmed that tenofovir is a mitochondrial toxin in renal tubular cells[40] and that exposure to tenofovir can result in renal injury in a small subset of HIV-positive patients. Additionally, research has documented a single-nucleotide polymorphism in the MRP-2 efflux transporter gene (*ABCC2*) in HIV positive patients who developed tenofovir-induced nephrotoxicity[41]. This is significant since tenofovir is transported via the organic anion transporter-1 (OAT-1) from the basolateral circulation into proximal tubular cells, where it is eventually translocated into the urine through apical efflux transporters such as multidrug resistance protein-2 (MRP-2) and MRP-4. This evidence coupled with the limited care for this disease in resource-limited settings makes it critical to prevent or slow progression to end-stage renal disease[42].

Regular measurement of kidney function in HIV-infected individuals at presentation and throughout tenofovir use is essential[10, 43]. The new South African ARV treatment guidelines recommend measurement of serum creatinine and creatinine clearance at ART initiation, at 3- and 6-months and yearly thereafter for patients on tenofovir[13]. Our results show median time to nephrotoxicity after tenofovir initiation is 3.6 months confirming the importance of that 3-month creatinine clearance. Only patients with a calculated creatinine clearance >50ml/min can safely start tenofovir[13]. If toxicity develops, the dosage interval of tenofovir can either be reduced to every 48 hours, bi-weekly or every seven days with haemodialysis. Alternatively, patients can be switched to zidovudine-lamivudine-efavirenz/nevirapine[13].

This study represents patients from only one government ART site, and may, therefore, not be generalizable to other clinics. Additionally, our findings should be considered in light of the study limitations. First, the exclusion of over 400 subjects due to missing creatinine clearance data could have introduced selection bias. However, besides having lower CD4 counts, the demographic and clinical characteristics of this group were similar to those included in the analysis. Second, the small sample size and few nephrotoxicity events

resulted in a lack of precision for this outcome in our study and may have limited our ability to accurately estimate this relationship. Third, urine and serum phosphate are not routinely measured, so the analysis was restricted to creatinine clearance as a measure of nephrotoxicity. Fourth, we acknowledged that the relationship between tenofovir and renal dysfunction in this analysis may have been confounded by the fact that patients with more advanced disease were using tenofovir during the first years the drug was available. Fifth, previous studies conducted on HIV-negative black populations found that the association between rate of renal events and baseline renal dysfunction was greater at creatinine clearance values <40 ml/min vs. 40 ml/min, suggesting that the nephrotoxicity attributed to tenofovir in our study may have been coincidental in some cases[44]. Finally, data on co-administration of nephrotoxic drugs and information about appropriate dose reduction of tenofovir were not available.

Conclusion

The high prevalence of kidney disease in South Africa[10, 11] coupled with starting all new ART initiates on tenofovir[13], highlights the need to screen patients for baseline renal dysfunction to reduce the burden of nephrotoxicity and improve treatment outcomes in this population. Additional research is needed to accurately assess the association between baseline renal insufficiencies and ART outcomes amongst patients on tenofovir.

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Table 1
Patient Characteristics at Tenofovir Initiation and Outcomes by 48-months of Follow-up of a Cohort in Johannesburg, South Africa stratified by Creatinine Clearance at Tenofovir Initiation (n = 890)

Characteristics	Creatinine Clearance			
	Normal (≥ 90 ml/min) (n=573)	Mild (60-89 ml/min) (n=271)	Moderate (30-59 ml/min) (n=46)	Total (n=890)
Sex				
Female	n (%)	186 (68.6%)	41 (89.1%)	654 (73.5%)
Male	n (%)	146 (25.5%)	5 (10.9%)	236 (26.5%)
Body Mass Index	median (IQR)	24.6 (21.5-28.2)	20.5 (18.0-23.1)	18.4 (16.0-21.0)
Age	median (IQR)	35.5 (31.7-41.0)	39.9 (34.5-46.5)	47.2 (34.4-53.9)
CD4 count at tenofovir initiation				
0-50 cells/mm ³	n (%)	53 (9.3%)	35 (12.9%)	13 (28.3%)
51-100 cells/mm ³	n (%)	33 (5.8%)	38 (14.0%)	8 (17.4%)
101-200 cells/mm ³	n (%)	100 (17.5%)	56 (20.7%)	10 (21.7%)
200-350 cells/mm ³	n (%)	154 (26.9%)	54 (19.9%)	6 (13.0%)
>350	n (%)	194 (33.9%)	69 (25.5%)	7 (15.2%)
Missing	n (%)	39 (6.8%)	19 (7.0%)	2 (4.4%)
WHO Stage				
I/II	n (%)	340 (59.3%)	145 (53.5%)	13 (28.3%)
III	n (%)	188 (32.8%)	92 (34.0%)	22 (47.8%)
IV	n (%)	45 (7.9%)	34 (12.6%)	11 (23.9%)
First-line ART Regimen				
d4T/3TC/EFV	n (%)	341 (59.5%)	161 (59.4%)	21 (46.7%)
d4T/3TC/NVP	n (%)	41 (7.2%)	16 (5.9%)	0 (0%)
3TC/TDF/EFV	n (%)	80 (14.0%)	54 (19.9%)	13 (28.3%)
Other	n (%)	111 (19.4%)	40 (14.7%)	12 (26.1%)
ART-naïve at tenofovir initiation				
Yes	n (%)	98 (17.1%)	73 (26.9%)	19 (41.3%)
No	n (%)	475 (82.9%)	198 (73.1%)	27 (58.7%)
Outcomes over 24-mos. of				

Characteristics	Creatinine Clearance				Total (n=890)
		Normal (≥ 90 ml/min) (n=573)	Mild (60-89 ml/min) (n=271)	Moderate (30-59.9 ml/min) (n=46)	
follow-up					
Diagnosed Nephrotoxicity	n (%)	4 (0.7%)	11 (4.1%)	6 (13.0%)	21 (2.4%)
Death	n (%)	30 (5.2%)	25 (9.2%)	14 (30.4%)	69 (7.8%)
Loss to follow-up	n (%)	52 (9.1%)	27 (10.0%)	7 (15.2%)	86 (9.7%)
Transferred out	n (%)	35 (6.1%)	13 (4.8%)	1 (2.2%)	49 (5.5%)
Alive and in care	n (%)	456 (79.6%)	206 (76.0%)	24 (52.2%)	686 (77.1%)
CD4 count (cells/mm ³) at tenofovir initiation	median (IQR)	273.5 (145-446)	188 (83-386.5)	109.5 (20-246.5)	245 (115-426)
Time on ART (months)	median (IQR)	37.0 (23.9-52.9)	34.7 (18.8-50.3)	25.5 (9.0-39.5)	35.8 (21.8-51.4)
Time from ART initiation to tenofovir initiation (months)	median (IQR)	14.0 (3.7-29.9)	10.1 (0.0-27.2)	1.3 (0.0-14.2)	12.5 (1.0-28.9)
Time on tenofovir (months)	median (IQR)	10.9 (6.9-16.8)	10.9 (5.6-16.0)	7.5 (1.8-16.7)	10.8 (6.5-16.6)
Hemoglobin (ug/dL)	median (IQR)	12.8 (10.5-13.9)	12.0 (9.6-13.6)	10.0 (8.2-12.5)	12.5 (10.0-13.7)

ART, antiretroviral therapy; BMI, Body Mass Index; IQR, interquartile range

Table 2
Crude and adjusted hazard ratios of nephrotoxicity and death by creatinine clearance level at tenofovir initiation among patients at Themba Lethu Clinic, Johannesburg, South Africa (n=890)

Nephrotoxicity[§]						
Creatinine clearance (ml/min)	Nephrotoxicity (n)	Person Time (years)	Rate/100 person-years	Crude HR (95% CI)	Adjusted HR[‡] (95% CI)	
Normal (≥ 90)	4	985.2	0.4	1.0	1.0	
Mild (60-89.9)	11	442.7	2.5	6.1 (1.9-19.2)	4.8 (1.5-15.2)	
Moderate (30-59.9)	6	56.2	10.7	27.5 (7.5-101.2)	15.0 (3.4-66.5)	
Nephrotoxicity[§] amongst ART-naïve patients initiated onto tenofovir						
Normal (≥ 90)	1	139.3	0.7	1.0	1.0	
Mild (60-89.9)	4	101.9	3.9	5.8 (0.6-53.5)	4.4 (0.4-45.8)	
Moderate (30-59.9)	3	25.3	11.9	18.0 (1.7-187.8)	14.3 (1.4-149.5)	
Nephrotoxicity[§] amongst ART patients switched onto tenofovir						
Normal (≥ 90)	3	845.9	0.4	1.0	1.0	
Mild (60-89.9)	7	340.9	2.1	5.6 (1.5-21.9)	5.3 (1.4-19.8)	
Moderate (30-59.9)	3	30.9	9.7	28.0 (5.5-141.7)	24.5 (3.2-188.2)	
Death[€]						
Normal (≥ 90)	30	988.9	3.0	1.0	1.0	
Mild (60-89.9)	25	453.8	5.5	2.0 (1.1-3.6)	1.2 (0.7-2.3)	
Moderate (30-59.9)	14	64.0	21.9	7.8 (3.8-15.9)	3.2 (1.3-7.8)	
Death[€] amongst ART-naïve patients initiated onto tenofovir						
Normal (≥ 90)	10	139.5	7.2	1.0	1.0	
Mild (60-89.9)	10	101.9	9.4	1.7 (0.6-4.6)	1.2 (0.4-3.4)	
Moderate (30-59.9)	7	29.1	24.0	3.9 (1.2-12.9)	1.6 (0.4-6.6)	
Death[€] amongst ART patients switched onto tenofovir						
Normal (≥ 90)	20	849.4	2.4	1.0	1.0	

Nephrotoxicity [§]					
Creatinine clearance (ml/min) [‡]	Nephrotoxicity (n)	Person Time (years)	Rate/100 person-years	Crude HR (95% CI)	Adjusted HR [‡] (95% CI)
Mild (60-89.9)	15	346.9	4.3	1.9 (0.9-3.9)	1.2 (0.6-2.7)
Moderate (30-59.9)	7	34.9	20.1	9.1 (3.7-22.4)	5.2 (1.6-17.0)

CI, confidence interval

[§]Nephrotoxicity was defined decline in kidney function from baseline (acute or chronic) that is secondary to a toxin (including drugs)

[‡]Creatinine clearance was categorized according to the U.S. National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI)

[‡]Hazard ratios (HR) are from a marginal structural Cox hazard models adjusted for WHO stage III/IV, gender, age, CD4 count, BMI, ART-naive and haemoglobin at tenofovir initiation and current viral load status

[¶]Death obtained from South African National Vital Registration Infrastructure Initiative