

Impairment of Kidney Function among US Hispanics on Tenofovir

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Abstract

While Hispanic patients represent a growing segment of the HIV-infected US population, nephrotoxicity due to use of tenofovir disoproxil fumarate (TDF) has not been assessed in this patient group. We model the changes by assessing repeated measurements of serum creatinine in 106 male Hispanic HIV patients on tenofovir seen in a clinic in El Paso, Texas. We estimated changes in estimated glomerular filtration rates (eGFR) controlling for age, diabetes and hepatitis B chronic infection. We found a deficit in eGFR of 0.5 ml/min/1.73 m² (95% CI: -0.7, -0.4) per month using the Modification of Diet in Renal Disease (MDRD) equation and 0.4 ml/min/1.73 m² (95% CI: -0.5, -0.3) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. These findings are consistent with findings from studies reporting data on other ethnic groups that call for the need to monitor kidney function among persons on tenofovir.

Introduction

Tenofovir disoproxil fumarate (TDF), a nucleotide analogue reverse-transcriptase inhibitor is one of the most widely used antiretroviral medications and was approved by the US Food and Drug Administration for pre-exposure prophylaxis of primary human immunodeficiency virus (HIV) infection [1]. Although there is evidence that TDF impairs the renal function [2,3], previous studies have not reported the concurrent assessment of kidney function among TDF use in Hispanics. Hispanics comprise the largest ethnic minority group in the US and experience disproportionate burden of diabetes and kidney disease. For this reason, as part of a Phase IV safety study on the use of TDF among HIV-infected Hispanic men who have sex with men, we conducted a pharmacovigilance retrospective study in El Paso, Texas, a predominantly Hispanic community. The specific objective of the study was to assess the effect that TDF has on estimated glomerular filtration rates among US Hispanics.

Population and Methods

This study was approved by the University of Texas at El Paso Institutional Review Board (80204-1); only de-identified data was made available to the investigators.

The study population consisted of HIV patients who took part in the above-mentioned Phase IV study and received care at La Fe Care, a Federally Qualified Health Center, which provides medical services to underserved communities throughout the region of El Paso, Texas. Study personnel abstracted data on demographics, laboratory assessments and start dates for TDF medications. In total, 117 male patients on TDF were evaluated; 11 of these were excluded due to having less than 6 months of TDF therapy. The analytic study was comprised of 510 observations from 106 individuals receiving TDF from 2004 to 2006.

We estimated the glomerular filtration rate (eGFR) at each visit using a reduced version of the Modification of Diet in Renal Disease Study (MDRD) equation: $eGFR = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age in years})^{0.203}$ [4]. We also used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [5] formula to estimate eGFR.

The authors used repeated measures mixed modeling to estimate the changes in eGFR for each patient and across the cohort. These

models adjusted for age at baseline, and reported diabetes, as well as the presence of hepatitis B surface antigen (HBsAg). Statistical significance was defined as two-sided *P*-values < 0.05. We conducted all statistical analyses in SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 106 patients were followed anywhere from 6 months to 36 months (typically for 16 months, interquartile range=11-25). Almost forty-percent of participants were followed for at least 2 years. Participants were typically middle aged (median=42 years, interquartile range=37-47). Ten percent had been diagnosed with diabetes mellitus, while 8.5% were chronic carriers of HBsAg (Table 1). None of the participants was concomitantly receiving other nephrotoxic drugs commonly prescribed to HIV patients such as amphotericin B, cidofovir, foscarnet, pentamidine [5], and only one patient received acyclovir during the study period.

At baseline, the typical participant of this study population had an eGFR MDRD of 91.4 (SD=22.5), and based of CKDEPI a mean eGFR of 97.3 (SD=18.6). Depending on the equation used, there were 8 subjects (7.6%) using CKDEPI or 9 subjects (8.5%) using MDRD with eGFR below 60 mL/min, one cut-off value for screening of chronic kidney disease.

Table 2 describes the results of the mixed model regression analyses using both the MDRD and CKDEPI equations. These analyses took into account the individual tracking on kidney function (i.e., serum creatinine) and adjusted the mean change in eGFR (according to

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Characteristic	Mean (SD)	Range	Number	(%)
Age (years)	42.6 (8.6)	25-70		
20-29			6	5.7
30-39			31	29.2
40-49			51	48.1
50-59			14	13.2
60-69			2	1.9
70+			2	1.9
Months on Follow-Up (Months)				
6-11			24	22.6
12-23			39	36.8
24-36			43	40.6
Diabetes			11	10.4
Hepatitis B Infection			9	8.5
Estimated Glomerular Filtration Rate (mL/min) MDRD	91.4 (22.5)			
Estimated Glomerular Filtration Rate (mL/min) CKDEPI	97.3 (18.6)			

Table 1: Baseline characteristics of 106 HIV infected Hispanic Men receiving Tenofovir, 2004, El Paso, Texas.

A. Estimates based on the MDRD equation.

All variables entered in the model	β (95% CI)	Mean eGFR	SE	P-value
Age				
24-38	Referent	86.6	4.6	0.4
39-45	-4.6(-11.7, 2.5)	85.5	4.1	
46-70	-1.2 (-7.0, 4.5)	81.9	4.3	
Diabetes				
Yes	-10.5 (-22.7, 1.6)	79.4	6.4	0.09
No	Referent	89.9	3.1	
Hepatitis B Virus Surface Antigen				
Present	-4.5 (-14.2, 5.1)	82.3	5.8	0.4
Absent	Referent	82.3	3.1	
Time on Follow-Up (Months)	6-36	-0.5 (-0.7, -0.4)		P<0.001

B. Estimates based on the CKDEPI equation.

All variables entered in the model	β (95% CI)	Mean eGFR	SE	P-value
Age				
24-38	Referent	86.3	3.5	0.08
39-45	-3.4(-8.8, 2.0)	90.5	3.3	
46-70	-7.6(-14.2, -0.9)	93.9	3.7	
Diabetes				
Yes	-12.9 (-22.9, -2.8)	83.8	5.2	0.01
No	Referent	96.7	2.5	
Hepatitis B Virus Surface Antigen				
Present	-4.0(-14.5, 7.5)	88.5	4.7	0.4
Absent	Referent	92.0	2.5	
Time on TDF (Months)	6-36	-0.4 (-0.5, -0.3)		P<0.001

Table 2: Change in Estimated Glomerular Filtration Rate (ml/min) among HIV infected Hispanic male patients on Tenofovir by Months of Therapy and Select Characteristics, El Paso, Texas, 2004-2006.

MDRD, panel A, or CKDEPI, panel B) by age, diabetes and presence of HBsAg. We found statistically significant decreases in eGFR by month on TDF using either the MDRD [0.5 ml/min per every month on TDF (95% CI: 0.6, -0.1)], or the CKDEPI equations [0.4 mL/min per month on TDF (95% CI=-0.5, -0.3)]. Figure 1 depicts a multivariate mean value of eGFR over a 36 month period using the MDRD equation.

Discussion

In our cohort of Hispanic male HIV patients on TDF, a clinically and statistically significant reduction in renal function as measured by eGFR was observed. For perspective of these findings, Table 2 also shows that the effect of having a medical diagnosis of diabetes mellitus in our study population amounted to a 10-13 mL/min difference, a magnitude of decrease that can occur in two years on TDF if the observed relation were proven to be causal. To our knowledge, no previous published studies have evaluated the effects of TDF on renal function among Hispanic patients. In a retrospective evaluation, Rawlings et al. [6] reported the impact of TDF and comorbidities in the development of renal impairment in 323 patients, including 96 African Americans and 19 Hispanics. Such a small sample of Hispanics makes it difficult to draw any meaningful conclusions. Therefore; our study is the first to specifically describe the change in levels of eGFR among Hispanics on TDF.

A number of comprehensive reviews of published studies have given us detailed information regarding patterns and mechanisms of TDF-induced renal dysfunction [2,3]. In 2010, Cooper et al. [2] conducted a systematic review and meta-analysis of the effects of TDF on renal function. Based on their criteria they included 17 eligible studies, but only six studies reported changes in MDRD-eGFR (including 2,334 participants). The authors found a mean difference of 2.6 mL/min/1.73 m², although this difference was not statistically significant, and there was a high degree of heterogeneity across the studies. Demographic data for the six studies included in that meta-analysis appears to show samples that consisted only of White and African-American participants.

A more recent review by Hall et al. [3] points to the occurrence of TDF-associated nephrotoxicity as a common reason for HIV-related referral to renal services. Osteomalacia and hypophosphatemia are conditions considered to be associated with TDF use. They propose that mitochondrial toxicity may be an important mechanism underlying the TDF-associated kidney impairment and endorse the Infectious Disease Society of America guidelines for monitoring renal toxicity in persons on TDF: requiring measurements of eGFR, serum phosphate, and urine analysis at least every 6 months in patients with eGFR<90 ml/min/1.73 m², the use of other drugs eliminated through renal secretions, other co-morbid diseases such as diabetes and hypertension, and use of alternative protease inhibitor such as a ritonavir-boosted regimen [7]. Our findings suggest that these guidelines would be applicable to Hispanic patients on TDF.

Both reviews concluded that although the clinical significance was modest, TDF-containing ART regimens were associated with a significant loss of kidney function. One more recent observational study described changes of eGFR by each year on TDF and found changes consistent with our estimates: the mean losses observed during the first year were -3.0 and -4.0 ml/min/1.73 m² [8]. A separate study reports that direct measurements of TDF in plasma are correlated with decreased levels of eGFR [9]. The authors highlight the need for close monitoring of kidney function for patients on TDF. More compelling evidence from yet another observational study among persons without previous impairment of kidney function showed that improvement of kidney function followed the discontinuation of TDF and ritonavir [10]. Finally, the largest observational study found that anti-retroviral therapies that include TDF had a higher risk of chronic kidney disease [11]. Yet recent studies point out that the observed effect on eGFR may reflect the effect of TDF on tubular rather than glomerular dysfunction [12].

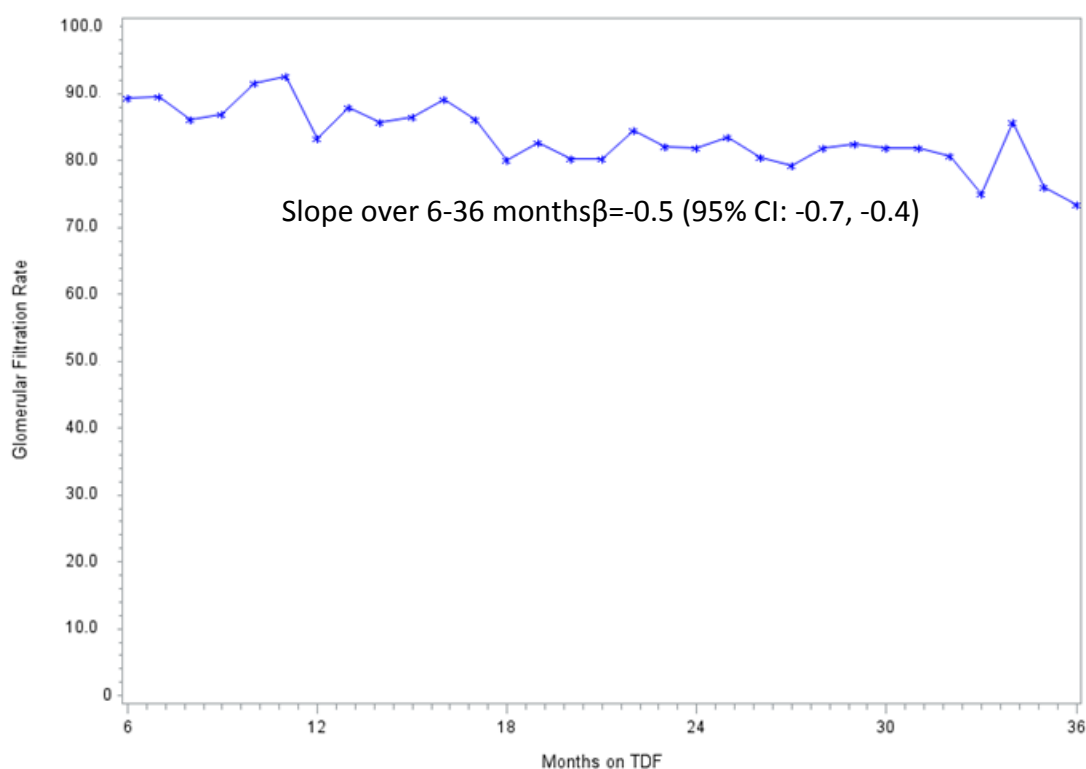


Figure 1: Multivariate mean value of estimated Glomerular Filtration Rates (MDRD eq.) by Months on TDF, Hispanic Men, El Paso, 2004-2006.

Limitations

One needs to consider at least three major limitations to this study when interpreting its findings: this was an observational, retrospective chart review cohort study, lacking a concurrent comparison group, and therefore potentially affected by unmeasured confounders. Data on non-nephrotoxic drugs and dietary components that have been identified as inhibitors of organic anion transporters was not collected; markers of tubule dysfunction such as glucose and phosphate in urine were not collected, nor were data on proteinuria. Also the history of blood pressure was sparse. In addition, the study sample size was relatively modest, and although observations in this study total over 500, they are based on only 106 study participants. In addition, the follow-up period was relatively short in comparison to other studies. Although none of our participants was taking any other potentially nephrotoxic drugs [6], one cannot rule out the possibility that other concomitant medications may have played a role.

Conclusions

In our retrospective review of HIV infected US Hispanic men on TDF, we found a modest but statistically significant reduction of eGFR (based on MDRD a decrease of 0.5 mL/min/1.73 m² per month or 0.4 mL/min per month using the CKDEPI). The effect of TDF use among Hispanics is similar to that reported among other ethnic groups. Our data support the notion that guidelines for routine monitoring of renal function should be applied to Hispanics patients on TDF therapy. In our opinion, the clinical significance of this reduction in eGFR may vary from patient to patient, but should be considered in Hispanic patients receiving TDF therapy.

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