Impact of Tenofovir on Renal Function in HIV-Infected, Antiretroviral-Naive Patients

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Objective: To better characterize the long-term effects of tenofovir on renal function in a large managed care organization.

Methods: We performed a retrospective cohort analysis in Kaiser Permanente for years 2002 to 2005 comparing renal function among antiretroviral naïve patients initiating a tenofovir-containing regimen (964 patients) or tenofovir-sparing regimens (683 patients). We evaluated glomerular filtration rate (GFR, [Modification of Diet in Renal Disease equation]), serum creatinine, and the development of renal proximal tubular dysfunction. We report multivariable hazard ratios (HR, Cox modeling) and linear outcomes (repeated measures) with predictors retained if $P < 0.10$ (backward selection). Potential predictor variables included in multivariate models were age, sex, Black race, baseline laboratories (including CD4 count), history of diabetes mellitus, hypertension, malignancy, hepatitis, and concurrent medications.

Results: Overall, tenofovir-exposed patients had a larger relative decline in GFR through 104 weeks (-7.6 mL/min/1.73 m^2 relative to tenofovir-sparing, $P < 0.001$); the degree of the difference varied by baseline GFR, with the greatest effect seen in those patients with GFR greater than 80 mL/min/1.73 m^2. Tenofovir-exposed patients had greater development of proximal tubular dysfunction over time (at 52 wk: $HR_{adjusted} = 1.95$ [$P = 0.01$] and at 104 wk: $HR_{adjusted} = 5.23$ [$P = 0.0004$]) and had greater risk of medication discontinuation ($HR_{adjusted} = 1.21$, $P = 0.02$), especially as renal function worsened. Viral control and CD4 count changes were similar between the two groups.

Conclusions: Tenofovir is associated with greater effect on decline in renal function and a higher risk of proximal tubular dysfunction in antiretroviral naïve patients initiating antiretroviral therapy.

Key Words: tenofovir, renal function, proximal tubular dysfunction, antiretroviral therapy

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INTRODUCTION

Tenofovir disoproxil fumarate is an oral prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor[1] that has been indicated for use in antiretroviral therapy (ART)-naïve patients.[2] However, tenofovir has been associated with renal failure and renal tubular dysfunction.[3,4] Several case reports have described the development of proximal tubular dysfunction in patients taking tenofovir.[5–11] The Swiss Cohort Study found tenofovir-associated renal function decline,[12] although other studies have not found increased incidence of renal dysfunction with tenofovir compared with other nucleoside reverse transcriptase inhibitors[1,13–16] or believed the effect to be limited.[17–21]

Renal dysfunction not specifically caused by particular ART drugs has been described in HIV-infected patients.[22–24] Some studies have indicated that renal dysfunction can be attributed to the other causes, including current or past medications.[11,14,25]

Potential renal toxicities of tenofovir have not been widely published in large clinical and managed care cohorts. The extensive prescription of tenofovir for antiretroviral naïve patients warrants longer-term studies with greater consideration of confounding variables, such as comorbidities and the other medications in the combination ART regimen. Here, we describe changes in renal function in ART-naive patients on tenofovir-containing and -sparing regimens with follow-up through 104 weeks. We consider important confounders such as patient demographics, comorbidities, and other medications prescribed.

METHODS

Study Design

We performed a retrospective cohort analysis of HIV-infected patients in three states (California, Maryland, Virginia) and the District of Columbia. All patients were enrolled in the Kaiser Permanente (KP) health maintenance organization and were initiating a first ART regimen from

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The principal investigator and co-authors had full access to all of the data in the study and takes responsibility for the integrity of the data, conclusions, and the accuracy of the data analysis.

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January 1, 2002 through December 31, 2005. We defined an ART regimen using Department of Health and Human Services definitions.[2] We compared the effect of tenofovir with no tenofovir use in these patients on kidney function (defined as changes in glomerular filtration rate [GFR], serum creatinine [SCr], and development of proximal tubular dysfunction), HIV RNA control, CD4 cell count changes, discontinuation rates, and ART adherence using previously validated pharmacy refill adherence measures.[26,27]

Subjects

KP is an integrated health maintenance organization serving various geographic populations in the United States. Patients receive multidisciplinary team health care, including HIV specialty care. Data from KP indicate that members are very similar to the general population of that area with regard to age, sex, and race/ethnicity, with only slight underrepresentation of those in lower and higher income and education categories.[28] As a result, HIV-infected KP members reflect regional demographics of all persons with HIV/AIDS. For example, current KP Northern California HIV-infected patients are largely male (89.3%), men having sex with men (77.9%), and white (62.7%); these statistics are remarkably similar to demographics of reported AIDS cases in California.[29]

We queried HIV registries and other appropriate databases in three KP regions (Mid-Atlantic, Northern California, and Southern California) to identify eligible patients. We captured patient demographics, hospitalization and outpatient visit diagnoses, laboratory results, and medications dispensed using electronic databases. Subjects were HIV-infected patients over 17 years of age who had no evidence of prior ART use and initiated a first ART regimen during the specified time period. Additional inclusion criteria were HIV RNA greater than 75 copies/mL at regimen initiation, SCr measured within 90 days before regimen initiation, at least 6 months of KP membership before the regimen, and patient receipt of laboratory testing and medications in KP. Patients were excluded if they had prior evidence of any antiretroviral medication use, a prior history of renal disease or dialysis (history of nephrolithiasis was permitted), or they had no follow-up laboratory or pharmacy data. Patients were followed through the earliest of KP membership termination, death, or end of study.

Measurements

We queried appropriate databases for the following baseline values (≤90 days of regimen initiation): sex, age, race, HIV RNA levels ($\log_{10}$/mL), CD4 cell count (no./μL), SCr (mg/dL), serum phosphate (mg/dL), serum bicarbonate (mEq/L), evidence of proteinuria (≥1+ qualitative or ≥30 mg% quantitative), serum uric acid (mg/dL), and evidence of glucosuria (≥1+ qualitative or ≥30 mg% quantitative) in the presence of normal serum glucose (<120 mg/dL). Baseline laboratory values were the values recorded closest before (or within 5 days after for non-HIV related measures) the regimen initiation date.

We recorded all laboratory values and antiretroviral medication prescription fills/refills from the initiation date through the end of the study period. GFR was calculated using the four-variable Modification of Diet in Renal Disease formula.[30,31] Adherence to ART over the observation period was calculated using established methods developed for administrative pharmacy databases. These methods account for all of the component medicines of an individual patient's ART regimen.[32,33] Adherence is computed across all antiretroviral doses in an interval (bounded by a first and last fill date of drug and last supply) for which the patient has the drug in possession (based on quantity supplied and dosing in the interval between fills) as a percentage of total intended doses. Using pharmacy records to ascertain ART adherence has been used and validated in previous studies at other institutions and KP.[26,34] Discontinuations were recorded if the ART regimen from the initiation date was different at censor date or if tenofovir was discontinued. The ART regimen was censored at date of discontinuation for the adherence calculations.

Data Analysis

Our primary predictor of interest was presence or absence of tenofovir 300 mg in the ART regimen analyzed. We measured adherence to ART through 52 and 104 weeks, changes in SCr (linear basis or elevation to >2.0 mg/dL), GFR (linear basis or ≥50% decline from baseline), CD4 cell count, achieving HIV RNA less than 75 copies/mL, and development of proximal tubular dysfunction. For the outcomes SCr greater than 2.0 mg/dL or GFR 50% or greater decline, we required this result on two consecutive measures but used the first date recorded for analytic purposes.

The development of proximal tubular dysfunction can lead to the following perturbations: proteinuria (defined as at least 1+ or 30 mg% on urine dipstick), glucosuria (at least 1+ or 30 mg%) in the presence of normal serum glucose, hypophosphatemia (<2.7 mg/dL), or phosphaturia, serum acidosis (serum bicarbonate <24 mEq/L), hypokalemia (<3.5 mEq/L), and hypouricemia (<2.0 mg/dL). People need usually two or greater manifestations to indicate the presence of proximal tubular dysfunction.[35,36] We required that greater than two manifestations occur within a 30-day window of each other to meet diagnostic criteria for proximal tubular dysfunction. All patients were evaluable for this phenomenon.

We analyzed continuous outcomes of changes in GFR, SCr, and CD4 cell counts through repeated measures linear mixed models. We used Cox proportional hazard modeling for dichotomous outcomes of GFR 50% or greater decline, SCr greater than 2.0 mg/dL, development of proximal tubular dysfunction, achieving HIV RNA less than 75 copies/mL, or discontinuation or change of ART from initiation date.

Potential predictor variables included demographics (age, sex, Black race [yes/no]); baseline creatinine and CD4 cell count; history of diabetes mellitus, hypertension, malignancy, or co-infection with hepatitis B or C; ART regimen class (protease inhibitor [PI], non-nucleoside reverse transcriptase inhibitor, or mixed); or use of ritonavir, stavudine, didanosine, zidovudine, angiotensin converting enzyme inhibitor (or angiotensin receptor blocker), or diuretic. We used backward selection and excluded predictor variables with highest P values singly until the final model contained only predictor variables with $P < 0.10$.

We obtained approval from all KP regions' institutional review boards. The institutional review boards waived the

requirement for informed consent before the start of the study for all patients.

RESULTS

One thousand six hundred forty-seven patients were antiretroviral naïve and started on ART during the study period, of which 964 (58.5%) patients initiated tenofovir-exposed regimens and 683 (41.5%) initiated tenofovir-sparing regimens. At baseline, the tenofovir-exposed group was older (Table 1), but this was likely not a clinically significant difference. The tenofovir-exposed group had a greater prevalence of injection drug users and history of hepatitis B at baseline but not hepatitis C. Renal function at baseline and the prevalence of other comorbidities were similar. Because this was an observational study, we found diversity between the two groups with regard to the other antiretroviral medications and to ART regimen class in the ART regimen.

There was a statistically significant difference in adherence between the two groups (Table 2), although both groups had median adherence greater than 90% through 52 and 104 weeks. Both groups had a high percentage of patients achieving maximal viral control, which was not statistically different. However, the tenofovir-sparing patients had statistically significant greater declines in HIV RNA through 52 weeks but no statistically significant differences in CD4 cell counts at either 52 or 104 weeks (Table 2).

In unadjusted analysis, the tenofovir-exposed group had a statistically greater percentage of patients with GFR decline greater than 50% from baseline (4.8% for tenofovir exposed vs. 2.9% tenofovir-sparing; $P = 0.03$) but not SCr rising to greater than 2.0 mg/dL (2.9% tenofovir exposed vs. 1.9% others; $P = 0.12$).

In both unadjusted and adjusted analysis for mean change in GFR from baseline, the tenofovir-exposed patients had statistically significantly greater declines in GFR through

TABLE 1. Baseline* Values

Variable	Tenofovir-Exposed Group (N = 964)	Tenofovir-Sparing Group (N = 683)	*P*
Demographics			
Follow-up time from regimen initiation, mo†	27.6 (19.7, 39.6)	32.6 (20.9, 43.7)	<0.0001
Age at ARV initiation†	43.0 (37.9, 49.5)	41.5 (35.0, 49.0)	0.002
Male, n (%)	830 (86.1)	598 (87.6)	0.39
Black, n (%)	236 (24.5)	167 (24.5)	0.41
IDU as HIV risk behavior, (%)	30 (3.1)	13 (1.9)	0.02
Prior medical history, n (%)			
HBV	42 (4.4)	12 (1.8)	0.004
HCV	42 (4.4)	27 (4.0)	0.49
Diabetes mellitus	52 (5.4)	30 (4.4)	0.36
Hypertension	136 (14.1)	86 (12.6)	0.37
Malignancy	81 (8.4)	57 (8.4)	0.97
Baseline† laboratory value			
CD4 cell count (no./μL)†	206 (90, 296)	204 (84, 315)	0.07
HIV RNA (log_{10}/mL)†	4.8 (4.3, 5.2)	4.8 (4.4, 5.3)	0.22
Creatinine (mg/dL)†	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.89
GFR (MDRD formula, mL/min/1.73 m^2)†	99.8 (85.8, 115.6)	100.4 (85.9, 116.9)	0.52
Medication use			
History of ACE inhibitor use, n (%)	47 (4.9)	33 (4.8)	0.97
History of diuretic use, n (%)	47 (4.9)	26 (3.8)	0.3
Regimen class, n (%)			
Protease inhibitor (PI)	398 (41.3)	245 (35.9)	0.03
NNRTI	440 (45.6)	377 (55.2)	0.0001
Mixed (PI + NNRTI)	69 (7.2)	24 (3.5)	0.002
Co-administration, n (%)			
Indinavir	5 (0.5)	10 (1.5)	0.05
Ritonavir	451 (46.8)	189 (27.7)	<0.0001
Zidovudine	97 (10.1)	572 (83.8)	<0.0001
Stavudine	45 (4.7)	61 (8.9)	0.0005
Didanosine	187 (19.4)	44 (6.4)	<0.0001
Lamivudine	452 (46.9)	662 (96.9)	<0.0001
Efavirenz	398 (41.3)	327 (47.9)	0.008
Atazanavir	272 (28.2)	48 (7.0)	<0.0001

*Recorded less than 90 days before index date.
†Median (interquartile range).

TABLE 2. Antiretroviral Adherence, HIV RNA, CD4 Cell Count, and Risk of Regimen Discontinuation

Crude Results	Tenofovir-Exposed Group	Tenofovir-Sparing Group	*P*
ART adherence rate, median (IQR)			
Through 52 wk	94.0% (76.0, 100)	97.0% (83.1, 100)	0.0001
Through 104 wk	93.0% (74.0, 100)	96.4% (84.0, 100)	0.0002
HIV RNA < 75 copies/mL at end of follow-up, n (%)	655 (79.5)	427 (76.8)	0.26
Change in CD4 T-cell count no./μL, median (IQR)			
Through 52 wk	+156 (+68, +264)	+159 (+69, +259)	0.9
Through 104 wk	+179 (+65, +296)	+194 (+110, +326)	0.09

Multivariate Outcomes*	Tenofovir Group Compared with Tenofovir-sparing Group: Adjusted Model†	*P*
Change in HIV RNA from baseline value (log_{10}/mL)		
Through 52 wk	+0.12 (+0.05 to +0.18)	0.007
Through 104 wk	+0.03 (~0 to +0.14)	0.42
Change in CD4 T-cell from baseline value (count/μL)		
Through 52 wk	+1.9 (−12.8 to +16.6)	0.80
Through 104 wk	−8.6 (−23.9 to +6.7)	0.27
Discontinuation of regimen		
Adjusted hazard ratio	1.21 (1.03 to 1.42)	0.02

*Multivariate modeling by linear repeated measures for continuous outcomes and Cox proportional hazard modeling for dichotomous outcomes. Predictor variables included in full model: demographics (age, gender, Black—yes/no); baseline creatinine and CD4 cell count; antiretroviral status; history of diabetes mellitus, hypertension, malignancy, hepatitis B or C; use of ritonavir, stavudine, didanosine, zidovudine, ACE inhibitor, or diuretic. Final model developed by backward selection until all covariates were at $P < 0.10$ level.

†Results are mean estimate (95% confidence interval).

IQR, Interquartile range.

52 and 104 weeks compared with the tenofovir-sparing patients (Table 4 and Fig. 1). The decline in GFR was more pronounced among tenofovir-exposed if the baseline GFR was greater than 80 mL/min/1.73 m^2 but also significantly decreased if the GFR was between 50 and 79 mL/min/1.73 m^2. The risk of developing greater than 50% decline in GFR (Table 4) associated with tenofovir exposure approached statistical significance in the adjusted analyses. The only statistically significant predictors of greater than 50% decline in GFR or as a continuous outcome measure were increased age, diabetes mellitus, inclusion of PI class in regimen, and lower CD4 counts at baseline.

Increases in SCr were also statistically significant among tenofovir-exposed patients compared with tenofovir-sparing patients but not the risk of SCr rising above 2.0 mg/dL (Table 4). Statistically significant ($P < 0.05$) predictors of SCr rise were increased age and lower CD4 count. Among patients with baseline CD4 counts less than 50 cells/μL (289 patients), there was a significantly greater risk of developing SCr greater than 2.0 mg/dL with tenofovir-exposed compared with tenofovir-spared patients (adjusted hazard ratio [HR] = 8.84 [95% confidence interval: 1.11 to 70.06], $P = 0.04$).

We found a statistically significant higher proportion of tenofovir-exposed patients meeting criteria for proximal tubular dysfunction compared with tenofovir-sparing patients (7.6% and 4.2% respectively, $P = 0.006$). All components of the definition (Table 3) had a statistically greater incidence among the tenofovir-exposed patients, except for hypokalemia and hypouricemia, albeit individual components did not necessarily occur simultaneously. In adjusted analyses, the risk for proximal tubular dysfunction was significantly greater among tenofovir-exposed patients, which developed and increased over time (Table 4). Other significant ($P < 0.05$) predictors of development of tubular dysfunction were increased age, diabetes mellitus, PI-based regimen, and lower CD4 count at baseline. Only four tenofovir-exposed and one tenofovir-sparing patients had both proximal tubular dysfunction and 50% or greater GFR decline ($P = 0.41$ comparing both groups).

There was not a significantly greater number of discontinuations among the tenofovir-exposed group (437 compared with 296, $P = 0.45$). There was a trend for the tenofovir-exposed patients to be less likely have HIV RNA below limits of quantification at time of discontinuation (199 compared with 144, $P = 0.06$). However, in adjusted analysis, there was a greater risk associated with tenofovir exposure and discontinuation of the regimen (adjusted HR = 1.21 [1.03 to 1.42], $P = 0.02$). Of those who developed proximal tubular dysfunction, 15 (20.6%) discontinued tenofovir. Comparing the two groups, we observed a greater percentage of tenofovir-exposed patients with creatinine rising to greater than 2.0 mg/dL who discontinued their ART regimen compared with patients whose creatinine did not rise to greater than 2.0 mg/dL (tenofovir exposed: 82.1% discontinued with creatinine >2.0 mg/dL compared with 44.2% discontinued with creatinine ≤2.0 mg/dL [$P < 0.0001$], tenofovir sparing: 53.9% vs. 43.1%, respectively [$P = 0.44$]). We similarly saw greater discontinuation rates among tenofovir-exposed patients whose GFR decreased more than 50% as opposed to those whose GFR did not decrease by greater than 50% (tenofovir exposed: 69.6% discontinued compared with 44.1% [$P = 0.0007$], tenofovir spared: 50.0% compared with 43.1% [$P = 0.54$]).

TABLE 3. Unadjusted and Multivariable Adjusted Modeling for Renal-related Outcome Measures

	Comparing Tenofovir-Exposed with Tenofovir-Sparing*			
	Unadjusted	***P***	**Adjusted Model†**	***P***
GFR Decreased >50% from Baseline				
Hazard ratio	1.76 (1.04 to 2.98)	0.03	1.63 (0.96 to 2.76)	0.07
Change GFR (MDRD equation)‡				
Overall				
Through 52 wk	−7.2 (−8.8 to −5.5)	<0.001	−6.4 (−8.0 to −4.8)	<0.001
Through 104 wk	−8.4 (−10.1 to −6.6)	<0.001	−7.6 (−9.2 to −5.9)	<0.001
50 ≤ GFR at initiation ≤80				
Through 52 wk	−3.7 (−6.5 to −1.0)	0.007	−3.5 (−6.0 to −0.9)	0.008
Through 104 wk	−4.9 (−7.8 to −2.0)	0.001	−3.8 (−6.6 to −1.1)	0.006
GFR at initiation >80				
Through 52 wk	−7.4 (−9.3 to −5.4)	<0.001	−4.0 (−6.7 to -1.3)	0.003
Through 104 wk	−8.8 (−10.8 to −6.8)	<0.001	−5.5 (−8.2 to −2.7)	<0.001
Serum Creatinine Increased to >2.0 mg/dL				
Hazard ratio	1.68 (0.87 to 3.24)	0.12	1.65 (0.85 to 3.20)	0.14
Change in serum creatinine (mg/dL)				
Through 52 wk	+0.07 (+0.06 to +0.08)	<0.001	+0.03 (+0.02 to +0.05)	<0.001
Through 104 wk	+0.10 (+0.08 to +0.11)	<0.001	+0.06 (+0.04 to +0.08)	<0.001
Development proximal tubular dysfunction				
At 26 wk	1.35 (0.85 to 2.14)	0.20	1.19 (0.73 to 1.92)	0.48
At 44 wk§	1.87 (1.17 to 2.98)	0.008	1.61 (1.00 to 2.60)	0.04
At 52 wk	2.16 (1.31 to 3.55)	0.002	1.95 (1.17 to 3.24)	0.01
At 104 wk	5.55 (2.20 to 13.99)	<0.001	5.23 (2.08 to 13.1)	0.004

*Results are mean estimate (95% confidence interval).

†Multivariate modeling by linear repeated measures (clustering by patient and date) for continuous outcomes and Cox proportional hazard modeling for dichotomous outcomes. Predictor variables included in full model: demographics (age, gender, Black—yes/no); baseline creatinine and CD4 cell count; antiretroviral status; history of diabetes mellitus, hypertension, malignancy, hepatitis B or C; regimen class, use of ritonavir, stavudine, didanosine, zidovudine, ACE inhibitor, or diuretic. Final model developed by backward selection until all covariates were at $P < 0.10$ level.

‡Estimated GFR by MDRD (mL/min/1.73m^2) = $186 \times (\text{SCr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if Black).

§First week that there was a statistically significant difference between tenofovir-exposed and tenofovir-sparing groups (unadjusted and adjusted).

DISCUSSION

Our study indicates a statistically significant effect of tenofovir on renal function in antiretroviral naïve patients initiating combination ART. We found statistically significant decreases in GFR and increases in SCr, which appears progressive with time (albeit slowly). We also found that tenofovir exposure is associated with a significantly greater risk of developing proximal tubular dysfunction, the risk of which increased over the time span of our study. Our study is significant for its patient population size, persistence of the adverse renal effects with time, and ability to control for a variety of confounders potentially associated with renal

TABLE 4. Components of Proximal Tubular Dysfunction Criteria by Tenofovir Exposure

	No. Patients Meeting Criteria During Follow-up		
	Tenofovir-Exposed Group, N = 964 (%)	**Tenofovir-Sparing Group, N = 683 (%)**	***P****
Definition components			
Proteinuria ≥1+ or ≥30 mg%	225 (23.3)	81 (11.9)	<0.001
Glucosuria ≥1+ or ≥30 mg% (with normal serum glucose)	39 (4.1)	6 (0.9)	<0.001
Serum phosphate below lower limit of normal (<2.7 mg/dL) or presence of phosphate in urine	184 (19.1)	43 (6.3)	<0.001
Serum bicarbonate below lower limit of normal (<24 mEq/L)	295 (30.6)	155 (22.7)	<0.001
Serum potassium below lower limit of normal (<3.5 mEq/L)	159 (16.5)	106 (15.5)	0.60
Serum uric acid below lower limit of normal (<2.0 mg/dL)	7 (0.7)	4 (0.6)	0.73
>2 Components within 30 days of each other	73 (7.6)	29 (4.2)	0.006

*Comparing tenofovir exposed to tenofovir-sparing groups; χ^2 or Fisher's exact test.

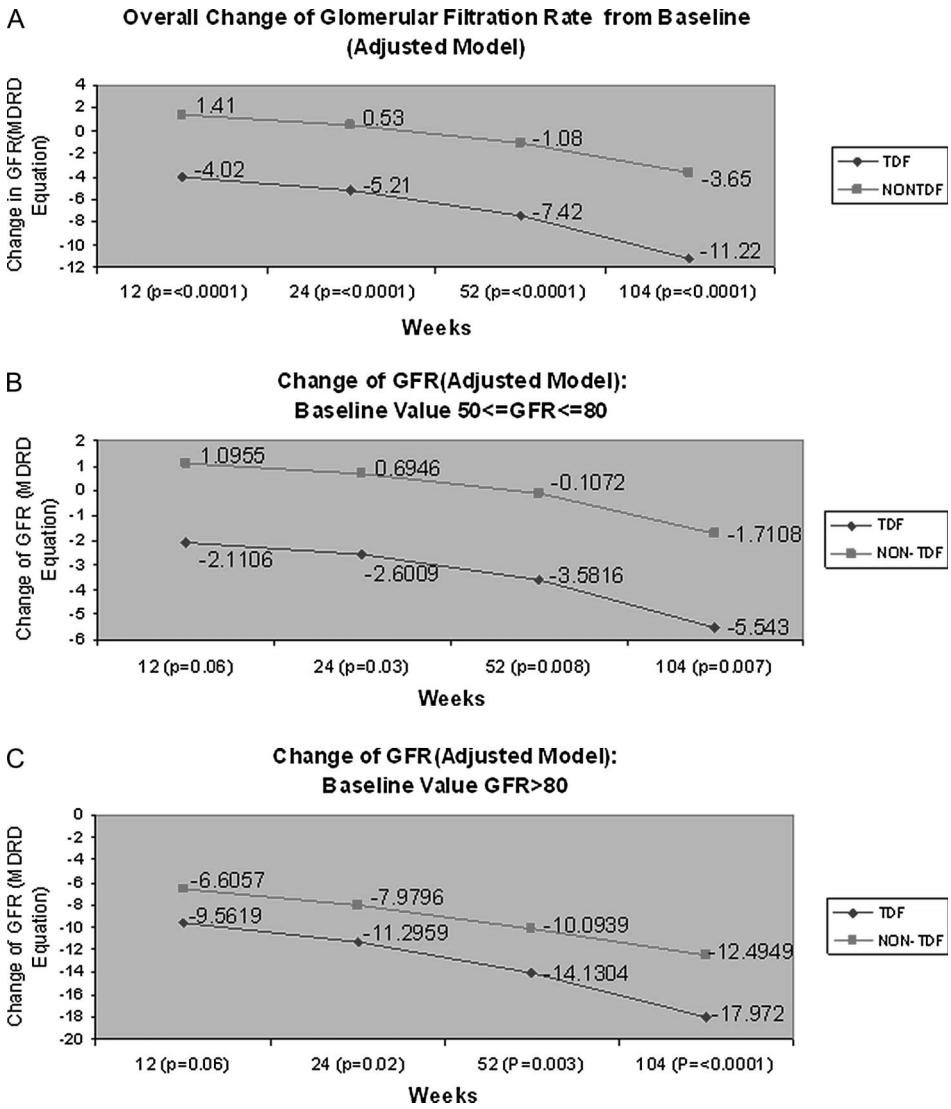

FIGURE 1. Change of glomerular filtration rate (GFR) from baseline by tenofovir exposure and baseline GFR.

dysfunction. To our knowledge, this is the largest cohort study of tenofovir-exposed compared with tenofovir-spared patients initiating ART.

Proximal tubular dysfunction has many manifestations, but there is no operational definition that has been applied to all tenofovir studies.[25,37,38] Most have adapted work from Izzedine and colleagues.[36] Here, tenofovir exposure was associated with a greater risk of developing proximal tubular dysfunction. Although we found a significantly higher incidence of tubular dysfunction with tenofovir-based ART than tenofovir-sparing ART, our result was fewer than that seen by Rodriguez-Novoa et al,[39] though they required fewer criteria. Just as noteworthy, four of the six potential manifestations of this perturbation were seen more frequently among tenofovir-exposed patients, although not necessarily concurrently. As recommended by others,[37,38] the components of tubular dysfunction should be checked regularly in patients taking tenofovir. Longer-term follow-up of patients who develop proximal tubular dysfunction but remain on tenofovir is needed.

Although it may appear that the decreases in GFR or rise in SCr are small on an absolute basis, they are worrisome because these deteriorations in kidney function could continue over time (as our data suggest by looking at the longitudinal results). Uniquely, we analyzed by baseline GFR and saw that the patients with the highest baseline GFR had the greatest declines in renal function with tenofovir exposure. Although there was some decline with tenofovir-sparing regimens, the continued rate of decline is much greater with tenofovir exposure. Other studies did not see an association of tenofovir exposure and significant decline in GFR or attributed adverse renal effects to other causes.[14,16,21] Unlike other studies,[16,21] we found the adverse renal effects of tenofovir persisted, even after controlling for a variety of potential other causes. Given the current commitment to long-term, even lifelong, ART, incremental small annual declines in kidney function could eventually lead to kidney failure and increased mortality.[40] This decline in kidney function may be even more pronounced as HIV-infected patients live longer with effective ART (including tenofovir-based regimens) and develop other

comorbidities that can impact renal function.[41,42] Thus, our results suggest a need for strategic use of tenofovir in HIV-infected patients, particularly those at high risk for adverse renal outcomes. In our study, higher-risk patients appear to have increased age, lower CD4 count at baseline, underlying diabetes mellitus, and PI-based regimens (although an effect was not noted among the individual specific medications in the PI class). The greater risk of GFR decline with PI use (compared with other regimen classes) has been previously described and is reassuring, given the readily available tenofovir-emtricitabine-efavirenz combination pill.[11] A further exploration of risk factors associated with renal function changes with tenofovir and ART is needed.

Fortunately, proximal tubular dysfunction and significant GFR decline do not appear to be concomitant. However, this could change with more prolonged use of medication.

More patients had maximal viral control at time of discontinuation among the tenofovir-sparing patients (although this is not statistically significant). This would imply that some of the discontinuations in the tenofovir-exposed group were for nonrenal-related reasons (i.e., virologic failure). However, the exact reason for regimen change/discontinuation was unavailable in our electronic databases. It is not surprising that incremental small changes in renal function would not evoke an immediate cause for concern to the clinician; it is quite possible many clinicians do not follow GFR but, rather, SCr. We did find a significantly higher rate of discontinuation among tenofovir-exposed patients at higher SCr levels. The relatively fewer discontinuations among the tenofovir-sparing patients with depressed renal function deserve exploration, as does even longer-term follow-up of our patients who remain on tenofovir despite GFR decline or proximal tubular dysfunction development.

Both groups demonstrated high ART adherence, good viral control, and substantial increases in CD4 cell counts over time. These results are especially reassuring because the tenofovir-exposed group had a larger number of hepatitis B co-infected patients and the association between HIV/hepatitis B coinfection and lower CD4 counts,[43,44] The comparable rises in CD4 counts is also reassuring because lower CD4 cell counts are associated with accelerated kidney disease.[45]

We recognize a few limitations with our study. Like all clinical cohort studies, not all patients received every test at every time point, and not all proximal tubular dysfunction components were measured in every patient. However, all patients had enough measured criteria to be eligible for analysis. We also could not explore the reasons for regimen discontinuation. Because this was an observational study, residual confounding is possible, such as the potential influences of other racial/ethnic groups other than black racial group or other medications that can impact renal function such as over the counter nonsteroidal anti-inflammatory drugs (which our electronic pharmacy records did not record).

In summary, tenofovir had a statistically significant and negative impact on renal function in our patient population. Tenofovir use also is associated with a significantly greater risk of developing proximal tubular dysfunction. We conclude that, although efficacious, the potential long-term adverse effects on kidney function may limit the use of tenofovir for patients at high risk for renal complications. Long-term monitoring of renal function and the components of proximal tubular dysfunction in patients taking tenofovir should be considered.

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