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No significant differences in nephrotoxicity for tenofovir combined with ritonavir-boosted protease inhibitors in treatment of adult HIV infection

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This study retrospectively evaluated specific changes in renal parameters among HIV-infected patients treated with regimens combining tenofovir (TDF) with ritonavir-boosted protease inhibitor (PI/r) compared with non-nucleoside reverse transcriptase inhibitor (NNRTI), with non-TDF regimens, and with those on no treatment before or during the study period. Patients in the treatment groups were included if they received the same regimen continuously for at least 12 months at our medical center during 2001 to 2008. Changes from baseline creatinine clearance and glomerular filtration rate were assessed at 6 and 12 months. A total of 625 patients met our criteria: 186 on TDF+PI/r, 182 on TDF+NNRTI, 151 on non-TDF antiretroviral regimens, and 106 on no treatment. Our patients were predominantly African-American men. Declines in creatinine clearance and glomerular filtration rate were not significantly different for PI/r versus NNRTI and for any TDF versus non-TDF treatment groups at 6 or 12 months. However, there was a significant decline in creatinine clearance for the treatment when compared with no treatment groups at 12 months (p=0.008) by a multivariate general linear model adjusted for covariates. In this study, no significant differences was found in nephrotoxicity among patients receiving TDF+PI/r compared with those on TDF+NNRTI and among those receiving TDF versus non-TDF regimens for 6 and 12 months.

Key words: Tenofovir, ritonavir, nephrotoxicity, renal toxicity, creatinine, creatinine clearance, glomerular filtration rate.

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) has been widely used in antiretroviral therapy (ART) since its approval in 2001 within the United States. TDF is renally excreted through glomerular filtration and active tubular secretion (Ray et al., 2006). Although prior case reports and observational studies described TDF-associated renal toxicity (Mauss et al., 2005; Malik et al., 2005; Zimmermann et al., 2006), prospective trials have demonstrated the relative safety of TDF with <1% patients having grades 3 and 4 creatinine (Cr) elevations (Pozniak et al., 2006; Izzedine et al., 2005). A meta-analysis of 17 prospective studies found little clinical effect despite some TDF-associated decline in glomerular filtration rate (GFR) (Cooper et al., 2010). Although TDF-treated patients had

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a greater decline in estimated GFR as compared to those taking other nucleoside reverse transcriptase inhibitors, these changes were mild and did not affect rates of TDF discontinuation (Gallant et al., 2005). However, TDF use has been associated with increased risk of proteinuria, rapid decline in kidney function, and development of chronic kidney disease (CKD) in the veteran population (Scherzer et al., 2012).

There have been conflicting reports regarding the safety of TDF in combination with a ritonavir-boosted protease inhibitor (PI/r), since co-administration with some PI/r-based therapies have increased plasma TDF concentrations by 20 to 30% (Kearney et al., 2006). Whether increase in plasma levels is due to decreased TDF renal clearance or increased TDF oral absorption remains unclear (Kiser et al., 2008; Jullien et al., 2005). From the California Collaborative Treatment Group, 35% patients treated with TDF+PI/r had increased renal toxicity when compared with regimens containing TDF combined with non-nucleoside reverse transcriptase inhibitor (NNRTI), or non-TDF-containing regimens (Goicoechea et al., 2008); this study of treatment-naïve and experienced individuals found that renal function steadily declined over 48 weeks of therapy in the TDF+PI/r group. The HIV outpatient study found no greater decline in renal function between the 99 patients treated with TDF+PI/r versus other TDF-containing regimens (Buchacz et al., 2006); this cohort included 309 treatment-naïve and experienced patients with similar demographic characteristics as the California Collaborative Treatment Group. From the Johns Hopkins HIV Database of ART-naïve patients, the group taking TDF+PI/r had a greater decline in GFR at 6 months than those taking TDF+NNRTI (Gallant et al., 2009).

In contrast to steady decline in GFR seen in the California Collaborative Treatment Group, GFR in the Johns Hopkins database patients stabilized at 12 and 24 months. The Swiss HIV Cohort Study found an additional decrease in GFR when TDF+PI/r using lopinavir or atazanavir when compared with TDF+NNRTI using efavirenz (Young et al., 2012). In their subsequent study, persons who initiated ART with TDF+PI/r using lopinavir or atazanavir and with TDF+NNRTI using efavirenz had similar rates of GFR declines and recovery when TDF was stopped (Young et al., 2014).

Our objective was to determine specific changes in the renal parameters of creatinine clearance and glomerular filtration rate in our patients with TDF+PI/r versus TDF+NNRTI, with TDF versus non-TDF-containing regimens, and with ART versus no ART.

MATERIALS AND METHODS

The Veterans Affairs (VA) Medical Center in Washington, DC is a tertiary care facility, which actively served more than 900 veterans with HIV infection annually during 2001 through 2008. This study was reviewed in accordance with the ethical standards on human experimentation and with the Helsinki Declaration of 1975 and its revision in 2000 and approved by our Human Studies Subcommittee and Research and Development Committee.

Study patients were retrospectively identified from the Clinical Case Registry for HIV at our VA Medical Center. This registry has collected data from 1985 to the present on HIV-infected veterans who received care within the VA Healthcare System. This registry provided information on patient demographics, underlying comorbidities, concomitant medications, and laboratory data. Comorbidities including renal insufficiency and renal failure were defined by use of codes from the Ninth Revision of the International Classification of Diseases within our registry. Subjects were divided into 4 groups based on their HIV treatment: TDF+PI/r, TDF+NNRTI, non-TDF-containing other ART regimens, and on no ART before or during the study period while in care at our facility. Patients in the treatment groups were included if they initiated an ART regimen at our medical center, had a continuous treatment regimen for at least 12 months, and had serum creatinine values available at baseline and after 6 and 12 months of therapy. Estimates of renal function were calculated using the Cockroft-Gault estimate for creatinine clearance (Cr Cl) and Modification of Diet in Renal Disease equation for estimated glomerular filtration; we chose to use 120 for any calculated values ≥120. Subject's actual weight was used in Cr Cl estimations. CD4 cell counts and HIV viral loads at 0, 6, and 12 months of therapy were also obtained.

Multivariate general linear models were used to test the effects of three different binary treatment variables on changes in outcomes using SAS (version 9.2, Cary, NC). Separate models were run for each treatment variable. The three treatment variables were: PI/r [TDF+PI/r coded Yes, TDF+NNRTI coded No; Other ART and No ART both coded missing]; Any TDF [TDF+PI/r and TDF+NNRTI coded Yes, Other ART coded No, No ART coded missing]; and Any ART [TDF+PI/r, TDF+NNRTI, and Other ART coded Yes, No ART coded no]. The outcome variables were: Cr Cl, estimated GFR, log HIV RNA, and CD4 count. Models were run separately for the change from time 0 to 6 months and time 0 to 12-months for each outcome variable.

RESULTS

During 2001 to 2008, a total of 625 patients met our inclusion criteria and were analyzed in 3 treatment groups: 186 on TDF+PI/r, 182 on TDF+NNRTI, and 151 on non-TDF-containing Other ART regimens. A control group of 106 patients, who had no ART experience before or during the study period at our facility, was included in our analyses. As shown in Table 1, race and gender were similar among all groups, as our patients were primarily African-American men. Patients in the non-TDF other ART and no ART groups were younger. No differences for baseline weight, non-steroidal anti-inflammatory drug (NSAID) use, and co-morbidities of diabetes, renal failure or dialysis, obstructive uropathy, and autoimmune disease were noted among the 4 groups. There was a trend toward less hypertension in the TDF+PI/r group. The non-TDF other ART group had higher rates of chronic hepatitis C and baseline renal insufficiency, but less use of sulfa/trimethoprim and other nephrotoxic drugs

As shown in Table 2, there were no significant changes on Cr Cl due to PI/r (p=0.39), any TDF (p=0.48), or any ART (p=0.18) from 0 to 6 months. From 0 to 12 months, the only significant change on Cr Cl was noted for any

Table 1. Summary of demographic and baseline clinical information for the four groups of patients on at least 12 months of treatment with tenofovir and ritonavir-boosted protease inhibitor (TDF+PI/r), tenofovir and non-nucleoside reverse transcriptase inhibitor (TDF+NNRTI), and non-tenofovir-based other antiretroviral therapy (Other ART), or were on no treatment (No ART).

Parameter	TDF+PI/r (n=186)	TDF+NNRTI (n=182)	Other ART (n=151)	No ART (n=106)
Demographics and weight				
Age (mean years ± SD)	48 ± 8	49 ± 11	45 ± 9	42 ± 10
African-American (%)	85.5	84.6	83.4	84.9
Male (%)	96.2	99.5	96.7	94.3
Weight (mean kg ± SD)	77.3 ± 13.8	80.2 ± 15.9	78.8 ± 14.6	83.2 ± 14.5
Antiretroviral-naïve (%)	5.4	22.0	70.2	100
Baseline comorbidities				
Hypertension (%)	28.5	39.0	37.1	40.6
Diabetes mellitus (%)	10.2	12.1	13.9	10.4
Hepatitis C (%)	27.4	20.3	35.1	44.3
Renal insufficiency (%)	4.8	2.2	11.3	5.7
Renal Failure or Dialysis (%)	3.2	1.1	5.3	5.7
Obstructive uropathy (%)	1.1	1.1	0.7	0
Autoimmune disease (%)	0	0	0	0
Nephrotoxic drugs				
NSAID use (%)	16.1	18.7	9.9	16.0
Sulfa /trimethoprim use (%)	37.1	22.0	17.9	2.8
Other drugs* (%)	60.2	55.5	23.2	45.3
Baseline HIV status				
CD4 (mean count/µl ± SD)	240 ± 193	397 ± 304	322 ± 230	627 ± 269
log_{10} HIV RNA (mean copies/mL ± SD)	4.4 ± 0.9	4.3 ± 1.1	4.2 ± 0.9	4.4 ± 5.0
HIV RNA below quantitation limit (%)	16.3	35.2	2.0	0

Other drugs included receipt of the following singly or in combination: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, cimetidine, acyclovir, aminoglycosides, cephalosporins, flucytosine, quinolones, and trimethoprim.

ART (p=0.008), while Cr Cl changes due to PI/r (p=0.50) and for any TDF (p=0.83) were not significant. Those patients who received any ART [TDF+PI/r, TDF+NNRTI, or other ART], had a mean decrease of 3.00 (95% confidence interval -9.30 to +3.26) ml/min, while those who received no ART had a mean increase of 2.90 (-3.90 to 9.80) ml/min. The estimated GFR showed no treatment effect for any of the three variables [PI/r, Any TDF or Any ART] from 0 to 6 months and from 0 to 12 months.

There were significant treatment effects on log HIV RNA for all three treatment variables [PI/r, any TDF or any ART] at each time point, although the effect for any TDF was only significant at a trend level [p=0.051] for 0 to 6 months. Change in CD4 count was not associated with any TDF at either time point, but was negatively associated with PI/r at both time points (p=0.03 at 6 months and p=0.002 at 12 months), and was positively associated with any treatment at both time points as expected.

DISCUSSION

During 2001 to 2008 for our population of predominantly African-American men with high prevalence of hypertension, diabetes mellitus, and chronic hepatitis C, no significant changes in both Cr Cl and GFR were observed between TDF+PI/r versus TDF+NNRTI groups and between any TDF versus non-TDF ART groups after 6 and 12 months. However, the only significant difference was seen for Cr Cl, but not GFR between any ART versus the no ART groups from 0 to 12 months. Our results are surprising as CKD and renal impairment have been increasingly recognized in the HIV-infected population, given 10 to 30% have microalbuminuria or proteinuria (Szczech et al., 2007), up to 10% have GFR <60 ml/min (Fernando et al., 2008), increased risk of renal dysfunction with later stages of HIV and with advancing age (Islam et al., 2012), and greater risk for kidney disease and rapid progression to end stage kidney

Table 2. Summary of comparisons for creatinine clearance (Cr Cl) calculated by the Cockroft-Gault estimate and glomerular filtration estimated: rate (GFR) by the Modification of Diet in Renal Disease equation as well as $\log_{10}$ HIV RNA and CD4 at 0 to 6 months and at 0 to 12 months.

Parameter	Time 0 to 6 months			Time 0 to 12 months		
PI/r versus NNRTI	**TDF+PI/r**	**TDF+NNRTI**	**p**	**TDF+PI/r**	**TDF+NNRTI**	**p**
Cr Cl (in ml/min)	-3.4 (-11.8 to 4.9)	-1.8 (-10.7 to 7.1)	0.39	-9.0 (-18.0 to 0.02)	-7.7 (-17.3 to 1.9)	0.50
GFR (in ml/min/1.73 m^2)	-7.4 (-17.0 to 2.3)	-5.9 (-16.0 to 4.4)	0.47	-13.3 (-23.7 to -3.0)	-12.5 (-23.5 to -1.5)	0.72
Log HIV RNA (in copies/ml)	-2.7 (-3.8 to -1.5)	-3.5 (-4.7 to -2.3)	0.0011	-2.8 (-4.0 to -1.6)	-3.8 (-5.1 to -2.5)	<0.0001
CD4 count (in cells/µl)	24 (-49 to 98)	70 (-7 to 147)	0.0026	49 (-27 to 125)	101 (21 to 183)	0.002
Any TDF	**TDF Groups**	**Other ART**	**p**	**TDF Groups**	**Other ART**	**p**
Cr Cl (in ml/min)	0.04 (-6.7 to 6.7)	-0.30 (-6.9 to 6.4)	0.48	-3.4 (-10.8 to 3.9)	-3.0 (-10.3 to 4.2)	0.83
GFR (in ml/min/1.73 m^2)	-2.2 (-9.8 to 5.4)	-0.9 (-8.4 to 6.7)	0.52	-6.2 (-14.4 to 2.0)	-4.5 (-12.6 to 3.6)	0.42
Log HIV RNA (in copies/ml)	-3.3 (-4.1 to -2.4)	-3.7 (-4.5 to -2.9)	0.051	-3.5 (-4.4 to -2.6)	-4.1 (-5.0 to -3.2)	0.0097
CD4 (in cells/µl)	64 (12 to 116)	59 (8 to 111)	0.74	66 (10 to 123)	89 (33 to 145)	0.12
Any ART	**All ART groups**	**No ART**	**p**	**All ART groups**	**No ART**	**p**
Cr Cl (in ml/min)	-1.5 (-7.4 to 4.3)	1.3 (-5.2 to 7.7)	0.18	-3.0 (-9.3 to 3.3)	2.9 (-3.9 to 9.8)	0.008
GFR (in ml/min/1.73 m^2)	-1.6 (-8.1 to 4.8)	-1.5 (-8.6 to 5.6)	0.94	-3.5 (-10.4 to 3.5)	0.25 (-7.4 to 7.9)	0.14
Log HIV RNA (in copies/ml)	-3.1 (-3.8 to -2.4)	0.07 (-0.7 to 0.8)	<0.0001	-3.4 (-4.0 to -2.6)	0.1 (-0.7 to 0.9)	<0.0001
CD4 (in cells/µl)	39 (-7 to 86)	-10 (-61 to 41)	0.0027	52 (3 to 102)	-38 (-93 to 17)	<0.0001

The antiretroviral treatment (ART) groups included patients on tenofovir (TDF) with ritonavir-boosted protease inhibitors (PI/r) versus non-nucleoside reverse transcriptase inhibitors (NNRTI), patients on TDF-based regimens versus non-TDF therapy (Other ART), and patients on Any ART versus No ART. The changes from 0 to 6 months and from 0 to 12 months are given with 95% confidence intervals and adjusted for covariates, where a positive number indicates an increase from month 0 to either month 6 or month 12. Significance of the change was tested using a general linear model, adjusted for race, gender, hepatitis C, chronic renal insufficiency, hypertension, diabetes mellitus, sulfa drugs, CD4 count, and log HIV RNA at time 0.

disease among African-Americans with and without HIV (Freedman et al., 1999; Lucas et al., 2008). At baseline, our 3 treatment groups had low CD4 count and high viremia which are additional risk factors for kidney disease (Winston et al., 2008; Fine et al., 2007). Similar to HIV-infected veterans nationwide (Goulet et al., 2007), most of our patients had one or more significant comorbid conditions.

TDF is one of the most frequently used ART agents within the entire VA Healthcare System. Among 989 patients in HIV care at our medical center during 2008, 8% received TDF, 21 efavirenz/emtricitabine/TDF and 24% emtricitabine/TDF. The introduction of highly active ART was correlated with declining CKD in the HIV-infected population, as viral suppression led to improved GFR (Lucas et al., 2004).

However, complications of longstanding treatment have had important impacts on ART-induced metabolic changes on the kidney and the direct renal effects of ART. Small case series and observational studies first described TDF-related nephrotoxicity (Mauss et al., 2005; Malik et al., 2005; Zimmermann et al., 2006). Although early clinical trials showed similar rates of nephrotoxicity between TDF and non-TDF controls (Gallant et al., 2004; Arribas et al., 2008), newer long-term studies found mild-moderate nephrotoxicity with consistent TDF use (Monteagudo-Cho et al., 2012). TDF has had a good safety profile, with low absolute rates of renal dysfunction or adverse events in treatment-naïve and experienced patients (Jones et al., 2004; Moreno et al., 2006; Guaraldi et al., 2009). Even with mild renal dysfunction, toxicity has been rarely clinically

significant and discontinuation rates low (Gallant et al., 2005; Young et al., 2007). For 226 patients in a single Singapore cohort, the median change in Cr Cl from baseline was -3.9 ml/min at 12 months and -3.6 ml/min at 24 months after TDF initiation (Chua et al., 2012). However, similar changes were found in Cr Cl of-3.4 ml/min for patients on any TDF versus -3.0 ml/min for those on non-TDF other ART after 12 months.

Despite the potential for nephrotoxicity, our data showed no significant reductions in renal function due to TDF+PI/r compared to TDF+NNRTI and any TDF compared to the non-TDF ART. PI/r based therapies have been reported to increase systemic TDF levels (Kearney et al, 2006); therefore, TDF+PI/r may lead to clinically significant renal toxicity due to proposed mechanisms of decreased renal clearance (Kiser et al., 2008; Jullien et al., 2005) and increased oral absorption (Tong et al., 2007). In addition, ritonavir could inhibit tubular secretion of TDF due to inhibition of the multidrug resistance associated protein (MRP-2) transporter (Izzedine et al., 2005), but TDF appears to be a substrate of MRP-4, which is not inhibited by ritonavir (Ray et al., 2006).

Differences between our study and previous publications may lie in our patient selection, sample sizes, time on TDF and the prevalence of HIV-associated nephropathy. The California Collaborative Treatment Group cohort (Goicoechea et al., 2008) was smaller with 146 patients and had fewer African-Americans than our study or the Johns Hopkins database (Gallant et al., 2009). Patients from the California Collaborative Treatment Group (Goicoechea et al., 2008) also had lower median age, lower baseline CD4 counts, and more ART-naïve patients than the HIV Outpatient Study cohort (Buchacz et al., 2006) or our study. Although their sample size included 309 patients, the HIV Outpatient Study (Buchacz et al., 2006) excluded patients with any baseline renal disease, had only 36% patients in the PI-based comparator group, and included no non-TDF control group. Among ART-naïve patients within the Kaiser Permanente cohort, greater relative decline in GFR were seen through 104 weeks for 964 exposed to TDF compared to 683 not exposed (Horsberg et al., 2010). A recent retrospective report found significant decrease in mild and moderate renal dysfunction among African HIV-infected adults after a median 2-year follow-up from ART initiation including those treated with TDF (Mpondo et al., 2014). Improvement in renal function in this study may be related to ART treatment of underlying HIV-associated nephropathy among patients in the Tanzania cohort. In contrast, our patients on no ART had a higher Cr Cl and GFR from 0 to 12 months compared to those who received any ART, although only the change in Cr Cl reached statistical significance.

Our study had several limitations. This was a retrospective assessment with notable differences among treatment groups in our observational database. Chronic renal insufficiency was greater at baseline for the non-TDF group, perhaps due to clinician caution in avoiding TDF in patients with known underlying renal disease. Among our 3 treatment groups, 70% of persons in the non-TDF group were naïve to ART at baseline. Clinicians may have avoided TDF-containing regimens as these patients also had higher prevalence of comorbidities such as diabetes mellitus, hepatitis C, chronic renal insufficiency, renal failure/dialysis compared to the other two treatment groups. The higher CD4 counts in the ART-naïve group were expected, since patients with lower CD4 counts would have warranted treatment. The nephrotoxicity effects of TDF were not seen in our patients within 12 months as earlier studies had predicted, but extending our study beyond 12 months would have decreased our group sample sizes and reduced the power of our analyses.

Conclusions

No significant differences in nephrotoxicity after 6 and 12 month periods were seen among our patients receiving TDF+PI/r compared to TDF+NNRTI and those receiving TDF-based ART compared to non-TDF ART. Whether this can be extended to the general HIV-infected population awaits further study. Our data demonstrated the relative safety of TDF+PI/r within our clinic patients of predominantly African-American men with high prevalence of hypertension, hepatitis C, and diabetes mellitus comorbidities.

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Conflicts of Interest

All authors report no conflict of interest.

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