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Renal Function in HIV-infected Veterans on Tenofovir with and without Ritonavir Compared with Those on No Tenofovir and No Antiretroviral Therapy

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Abstract

Background: Tenofovir (TDF) is renally cleared by glomerular filtration and active tubular secretion. Previous studies have shown conflicting data regarding the safety of TDF in combination with a ritonavir-boosted protease inhibitor (PI/r) at times indicating that this combination raised plasma TDF levels by 20-30%.
Methods: Patients on TDF+PI/r or TDF+non-nucleoside reverse transcriptase inhibitor (NNRTI) for ≥12 months at our VA Medical Center were retrospectively compared with those who received no (naïve) or other antiretroviral agents (other ART) for differences in estimates of glomerular filtration rate at 0, 6 and 12 months using Modification of Diet and Renal Disease (MDRD) in ml/min/1.73m^2 and tested by analysis of variance using SAS version 9.2 (Cary, NC).
Results: Of the 1021 patients reviewed, 650 met our inclusion criteria into 4 patient groups. There were no significant differences in baseline demographics other than CD4 counts and baseline creatinine. However, renal function decline over time did not differ between groups.
Conclusion: TDF+PI/r compared with TDF+NNRTI, other ARV therapy and treatment naiveté was not associated with significant declines in renal function within 12 months. Although our patients were older, primarily African-American men with high prevalence of hypertension and diabetes, our data demonstrate the relative safety of TDF+PI/r.

Background

The nucleotide reverse transcriptase inhibitor, tenofovir disoproxil fumarate (TDF), has been widely used in the treatment of human immunodeficiency virus (HIV) infection since its FDA-approval as antiretroviral therapy (ART) in 2001. TDF is renally excreted through glomerular filtration and active tubular secretion. Although there are case reports and observational studies describing TDF-associated renal toxicity, prospective trials have demonstrated the relative safety of TDF. However, there have been conflicting published reports regarding the safety of TDF in combination with a ritonavir-boosted protease inhibitor (PI/r), since plasma concentrations of TDF are increased by 20-30% with co-administration of some PI/r-based therapies. Patients from the California Collaborative Treatment Group (CCTG) treated with TDF and PI/r had increased renal toxicity, the HIV Outpatient Study (HOPS) Cohort of patients found no greater decline in renal function, and with Johns Hopkins HIV Database ART-naïve patients, the group taking TDF and a PI/r had a greater decline in GFR than those taking TDF and an NNRTI at 6 months, but renal function stabilized at 12- and 24-month analyses.
The objective of the present study was to determine changes in renal function with TDF and PI/r co-administration in the veteran population. Comparison groups included patients receiving TDF with a NNRTI, patients on other non-TDF containing ART regimens and ART-naïve HIV-infected patients.

Methods

The Veterans Affairs Medical Center located in Washington, DC (VAMC-DC) is a tertiary care facility serving veterans in the greater metropolitan area of the District of Columbia. Study participants were identified from the Clinical Case Registry for HIV (HIV CCR) at the VAMC-DC, which actively serves more than 900 veterans with HIV infection annually. The HIV CCR provided information on patient demographics, underlying medical conditions and concomitant medications, in addition to HIV-related therapy, serum creatinine levels, CD4 counts and HIV viral loads. Subjects were divided into four groups based on HIV-treatment regimen: TDF + PI/r, TDF + NNRTI, other non-TDF-containing ART regimens, and ART-naïve. Patients were included if they had initiated a TDF containing regimen within the VAMC-DC, remained on a continuous consistent 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 at each time point, using the Cockroft-Gault (C-G) estimate for creatinine clearance and Modification of Diet in Renal Disease (MDRD) equation for estimated glomerular filtration. One way and repeated-measures analysis of variance using SAS version 9.2 (Cary, NC) were employed to compare groups within time periods and to assess differences in the rate of change over time between groups.

Results

Table1: Summary of demographic and baseline clinical information for the four groups of study patients monitored for at least 12 months.

Parameter	TDF + PI/r (n=186)	TDF + NNRTI (n=182)	Other ART (n=151)	ART Naïve (n=131)	p
Demographics					
Age (mean years ± SD)	48 ± 8	49 ± 11	45 ± 9	42 ± 10	<.001
African American	85.5%	84.6%	83.4%	85.5%	0.953
Male	96.2%	99.5%	96.7%	94.7%	0.091
Baseline antiretroviral-naïve	5.4%	22.0%	70.2%	100%	<.001
Baseline comorbidities					
Hypertension	28.5%	39.0%	37.1%	42.0%	0.061
Diabetes mellitus	10.2%	12.1%	13.9%	11.0%	0.773
Hepatitis C	27.4%	20.3%	35.1%	35.9%	0.005
Renal insufficiency	4.8%	2.2%	11.3%	6.9%	0.005
Renal Failure or Dialysis	3.2%	1.1%	5.3%	3.1%	0.179
Nephrotoxic drugs					
NSAID use	16.1%	18.7%	9.9%	15.3%	0.166
Sulfa /trimethoprim use	37.1%	22.0%	17.9%	3.1%	<.001
Other drugs*	60.2%	55.5%	23.12%	39.7%	<.001

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

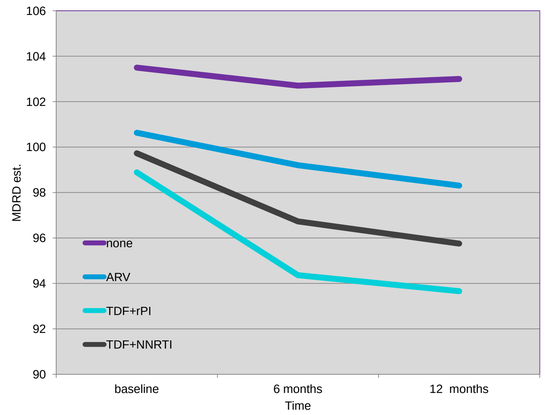
Results

Table 2: Summary of data at 0, 6 and 12 months for the 4 patient groups for creatinine, calculated creatinine clearance, estimated glomerular filtration, CD4 and virologic parameters.

PARAMETER	Time Point (months)	TDF + PI/r (n=186)	TDF + NNRTI (n=182)	Other ART (n=151)	ART Naïve (n=131)
Creatinine **	0	1.3 ± 1.5	1.1 ± 1.0	1.4 ± 1.7	1.2 ± 1.2
	6	1.4 ± 2.0	1.1 ± 0.9	1.4 ± 1.7	1.2 ± 1.1
	12	1.4 ± 1.9	1.1 ± 0.9	1.4 ± 1.4	1.3 ± 1.4
C-G creatinine clearance	0	97 ± 30	102 ± 33	102 ± 37	114 ± 36
	6	94 ± 31	100 ± 31	101 ± 35	115 ± 37
	12	93 ± 32	99 ± 32	100 ± 34	116 ± 38
MDRD glomerular filtration	0	99 ± 31	100 ± 24	101 ± 34	103 ± 29
	6	94 ± 30	97 ± 22	99 ± 34	103 ± 28
	12	94 ± 32	96 ±± 23	98 ± 33	103 ± 28
Mean CD4*	0	240 ± 193	397 ± 304	322 ± 230	640 ± 283
	6	304 ± 202	482 ± 294	399 ± 222	630 ± 299
	12	316 ± 204	504 ± 306	438 ± 226	604 ± 279
Undetectable VL* **	0	16.3%	35.2%	2.0%	17.8%
	6	52.8%	77.5%	67.5%	16.0%
	12	54.4%	81.9%	68.7%	11.5%
Mean log VL* **	0	4.4 ± 0.9	4.3 ± 1.1	4.2 ± 0.9	7.7 ± 2.0
	6	3.6 ± 1.1	3.3 ± 1.2	3.0 ± 0.9	7.8 ± 2.1
	12	3.6 ± 1.2	3.4 ± 1.2	3.1 ± 0.9	8.0 ± 2.2

P values are for the group x time interaction, which indicates whether treatment groups differ in the slope of change over time. *p<.05, **p<.01, ***p<.001

Figure: Change in estimates of renal function over time, calculated by Modification of Diet in Renal Disease equation



Conclusions

TDF is one of the most frequently used ART agents within VHA such that 2,865 received tenofovir, 4,691 efavirenz/emtricitabine/tenofovir, and 6,104 emtricitabine/tenofovir of 18,670 Veterans with ART prescriptions in 2008. While the safety of TDF itself has been well documented, PI/r based therapies have been reported to increase systemic TDF levels; therefore, the combination of TDF and PI/r may lead to clinically significant renal toxicity. The mechanism of increased TDF exposure is not completely understood; decreased renal clearance and increased oral absorption are proposed mechanisms. Despite the potential for nephrotoxicity, our data showed that the TDF + PI/r combination had no significant reduction in creatinine clearance or estimates of renal function compared with other HAART with and without TDF during a 12-month treatment period.

In conclusion, our data demonstrated the relative safety of TDF+PI/r among our clinic patients of primarily African-American men with high prevalence of hypertension and diabetes.

The views expressed are solely those of the authors and do not reflect the policies of the Department of Veterans Affairs or The George Washington University.

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