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Effect of Discontinuation of Tenofovir Disoproxil Fumarate (TDF) on Renal Function in Elderly Veterans

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ABSTRACT

Intro: A new formulation of tenofovir with alafenamide (TAF) has been introduced that promises to reduce the risk of renal disease. However, the clinical impact of TAF in elderly persons with HIV/AIDS and comorbid renal disease has not been fully investigated. Using patient data from Louis Stokes Cleveland VA Medical Center, this study examines the effect of TDF discontinuation on renal function.

Methods: With IRB approval, clinical data from 272 veterans with HIV/AIDS were gathered to estimate glomerular filtration rate (eGFR) using CKD-EPI (CE) and Cockcroft-Gault (CG) formulae.

Results/conclusions: patients were excluded because they did not meet the criteria for the study or for insufficient data. The remaining 150 patients had a mean age of 57.7 years, 96.7% were male, 51% African American, 50% were smokers, 28% had diabetes and 63% had vascular disease risk factors. Baseline mean sCr value was 1.1±0.3. Mean CD4 was 672 ± 372 on TDF containing regimens (703 ± 344 after switch) and 66% (69%) had viral loads <20 cp/mL. Serum creatinine (sCr) values before and after the discontinuation of TDF were collected, and eGFR and rate of change for eGFR and sCr were calculated. In a univariate manner, variables were also examined within 3 subgroups: smokers, diabetics and patients with vascular disease risk factors. Changes in boosting medication were rare (5 patients started cobicistat and 7 patients discontinued ritonavir) and thus had little effect on average changes in sCr and eGFR in this cohort. Overall, discontinuation of TDF stabilized sCr (Figure 1). Mean sCr increased by 0.13 and eGFR declined by 5.755 (CE) or 11.822 (CG) during the mean 181 days of observation prior to TDF discontinuation. After the switch, mean sCr increased by 0.002 during a mean of 396 days of observation; eGFR increased by 1.198 (CE) or 1.300 (CG). Similar trends were observed in the 3 subgroups. In all groups, discontinuation of TDF led to improvement in eGFR.

BACKGROUND

In July 2016, the US Department of Health and Human Services (DHHS) revised its guidelines for the treatment of persons living with HIV/AIDS so that the initial antiretroviral therapy (ART) recommended for treatment may contain an integrase inhibitor with 2 nucleoside reverse transcriptase inhibitors (NRTIs), often as a single tablet regimen (STR), or a boosted protease inhibitor (PI) regimen. In addition, a new formulation of the NRTI, tenofovir disoproxil fumarate (TDF), now tenofovir alafenamide (TAF), has been introduced that promises to reduce rates of osteoporosis, chronic kidney disease and renal tubular acidosis. The full impact of these newer agents outside of the clinical trials and DHHS policies has yet to be investigated, especially in regard to outcomes of comorbid conditions such as renal and bone diseases. Our previous research indicates that HIV positive veterans engaged in care are typically older, sicker, and have lower rates of adherence to non-HIV medications they take for chronic comorbid conditions (1). Using data from the Louis Stokes Cleveland Department of Veterans Affairs Medical Center Infectious Diseases PACT clinic, we examined the impact of the introduction of TAF and abacavir in STRs and in other ART regimens on adherence rates and outcomes for HIV treatment, and impact on renal disease and osteoporosis.

HYPOTHESES

Patients switched to newer ART regimens such as single tablet regimens (STRs) that do not contain TDF will demonstrate improvement in renal function as measured by estimated glomerular filtration rate (eGFR), and urine protein to creatinine ratio (UPCR)

They will also continue to have immune reconstitution and suppressed HIV viral loads, and decreased associated morbidity/mortality from HIV/AIDS. However, among older and sicker HIV infected persons, this improvement may be attenuated.

METHODS:

After obtaining IRB approval we used the VA Computerized Patient Record System (CPRS) to perform a retrospective and prospective chart review cohort study on patients seen in the CLE ID PACT clinics within the past 4 years (March 2013) and prospectively for 1 year (through February 28, 2018).

Data collected included patient age, gender, smoking, race, socioeconomic status, length of HIV infection, comorbid illnesses (cardiovascular, pulmonary, diabetes, chronic Hepatitis C treated and untreated, substance abuse, malignancy rheumatologic disease), and number of HIV vs. non HIV medications.

The study population was defined as veterans enrolled for HIV primary care in the CLE ID PACT clinics who received a TDF containing ART regimen through the previously specified period.

We will also extract or calculate eGFR using both the Cockcroft-Gault and CKD-EPI equations for any measures of serum creatinine, age and body mass (kg) following, or in the year preceding a change in ART from a TDF to a non TDF based regimen.

Because of possible independent effects on kidney function by boosted atazanavir and lopinavir containing regimens, and interactions between TDF and boosted protease inhibitors (PI-r or PI-cobicistat), we constructed mutually exclusive ART switch categories such as TDF/(non-nucleoside reverse transcriptase inhibitor(NNRTI) or INTEGRASE INHIBITOR)) → TAF/(NNRTI or INTEGRASE) or TDF/boosted PI → TAF/boosted PI.

We also collected any urine protein to creatinine ratio (UPCR) data available in this period.

Descriptive statistics were calculated for patient variables (mean age, % smokers, gender and race e.g.). Serum creatinine (sCr) values before and after the discontinuation of TDF were collected, and eGFR and a rate of change for eGFR and sCr were calculated (Δ eGFR/time). In a univariate manner, these variables were also examined within 3 subgroups: smokers, diabetics and patients with vascular disease risk factors.

RESULTS

Demographic data	
Mean age (yrs)	57.7
% male	96.7
% AA	51
% smokers	50
% with diabetes	28
%vascular dx risk	63
Baseline mean sCr	1.1 ± 0.3
Baseline mean CD4 on TDF	672±372
Mean CD4 after ART switch	703±344
Baseline % undet (<20cp/mL)	66%
% undet after ART switch	69%

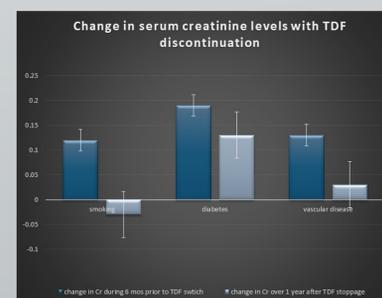


Fig 1 Average change in serum creatinine levels with TDF discontinuation in smoking, diabetes and vascular disease group 6 mos before the TDF switch (dark blue) and 1 year after switch (light blue)

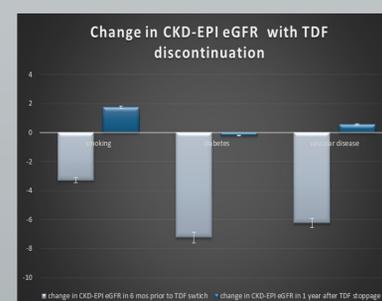


Fig 2 Average change in eGFRs calculated using CKD-EPI formula in smoking, diabetes and vascular disease group 6 mos before and 1 year after TDF discontinuation

- During the mean 181 days of observation before discontinuation of TDF, mean change in sCr was an increase of 0.13 and mean change in eGFR was a decline of 5.755 (CE) or by 11.822 (CG) in total study population.
- During the mean 396 days of observation after discontinuation of TDF, mean change in sCr was an increase of 0.002 and mean change in eGFR was an increase of 1.198 (CE) or by 1.300 (CG) in total study population.

RESULTS

	Δ in Cr	Δ in eGFR (CE)	Δ in eGFR (CG)
Smoking	0.121	-3.286	-10.459
Diabetes	0.187	-7.238	-8.071
Vascular Dz	0.128	-6.232	-11.225

Table 1 Mean changes in sCr and eGFR before the discontinuation of TDF

	Δ in Cr	Δ in eGFR (CE)	Δ in eGFR (CG)
Smoking	-0.031	1.746	0.525
Diabetes	0.126	-0.214	-0.050
Vascular Dz	0.028	0.567	0.040

Table 2 Mean changes in sCr and eGFR with the discontinuation of TDF

•A similar pattern of stabilization in sCr and eGFR was observed in all three subgroups. Patients in the smoking group showed mild improvement in renal function as their mean sCr decreased by 0.031 and eGFR increased by 1.746 (CE) and 0.525 (CG) with discontinuation of TDF. Patients with diabetes however, showed the least improvement with discontinuation of TDF. Mean change in sCr in diabetes group before the discontinuation of TDF was 0.187 and mean change in sCr with the discontinuation of TDF was 0.126.

CONCLUSIONS

- Discontinuation of tenofovir disoproxil fumarate led to stabilization of renal function in older HIV + veterans with renal disease.
- In all groups with renal disease risk factors, discontinuation of TDF led to improvement in eGFR with the largest effect in smokers and the lowest effect in persons with diabetes.
- Further studies using the national VA HIV cohort and using multilevel longitudinal models to estimate the effects of specific ART regimens on eGFR and UPCR, allowing multiple and sporadically-timed measurements within patient while controlling for both static and time-varying covariates including gender, age, smoking, race, duration of HIV infection, CD4, CD4/CD8 ratio, HIV viral load, cardiovascular, liver and pulmonary disease, diabetes, Hepatitis C co-infection, and use of other nephrotoxic medications are planned.

REFERENCE

1. Kodama F, Skalweit M, Burant C, Hirsch A. Differences in calculated adherence rates of ART and non-ART medications among HIV positive veterans. ID Week. San Francisco, CA; 2013.