Poster #2183

Outcomes of Tenofovir Discontinuation Among Human Immunodeficiency Virus (HIV)-Infected Patients with Suspected Tenofovir-Associated Nephrotoxicity

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Background

- Tenofovir disoproxil fumarate (TDF) is a widely recommended antiretroviral (ARV) for the first-line treatment of HIV infection[1]
- Systematic reviews and meta-analyses approximate a 1% yearly incidence of TDF-associated nephrotoxicity (TAN)[2]
- Limited published data exists regarding the reversibility of TAN after TDF discontinuation (d/c)
- A retrospective, cohort study of 24 male HIV-infected patients found 42% of patients had recovery to their baseline renal function, using the Modification of Diet in Renal Disease (MDRD) formula to estimate glomerular filtration rate (eGFR)[3]

Objective

- To describe outcomes of TDF d/c among HIV-infected patients with suspected TAN

Methodology

Study Design

- Single-center, retrospective, observational, cohort study of HIV-infected patients who had TDF d/c for suspected TAN from 2005 to 2015
- Approved by Wake Forest Baptist Health Institutional Review Board
- Inclusion: Treatment of HIV infection with a TDF-based regimen for at least 3 months prior to d/c, serum creatinine (SCr) ≥1.30 mg/dL within 3 months prior to TDF d/c, ≥1 SCr value within 1 week to 2 years after TDF d/c
- Exclusion: SCr >1.50 mg/dL within 3 months prior to TDF initiation, age <18 years, incomplete electronic medical record (EMR), and renal impairment secondary to other causes

Outcome Measures

- Renal function was estimated using Cockcroft-Gault (CG) and MDRD formulas
  - Prior to the initiation of TDF
  - At the time of TDF d/c
  - After TDF d/c, including a comparison of the overall best value within select time-frames: 1 week – 6 months, 6 months – 1 year, 1 year – 2 years, and 2 years – 5 years
- Recovery: percent of patients with a return to pre-TDF renal function
- Improvement: percent of patients with an increase in eGFR of ≥7 mL/min/m^2

Statistical Analysis

- Descriptive statistics
- Comparisons analyzed using Wilcoxon signed-rank test or paired t-test for paired continuous data, chi-square for independent categorical data, and t-test for independent continuous data
- Time-to-event analysis to assess speed of improvement and recovery
- Cox proportional hazards model to assess factors associated with recovery

Results

- Between 2005 and 2015, 109 patients had TDF d/c for suspected TAN
  - There were 49 patients excluded for the following reasons: incomplete EMR (n=19), renal impairment secondary to other causes (n=18), SCr >1.50 mg/dL within 3 months prior (n=8), age <18 years (n=1), and multiple exclusion criteria (n=3)
  - A total of 60 patients met eligibility criteria

Table 1. Patient and treatment characteristics

Characteristic (n=60)	Result
Age, years, mean ± SD	50.9 ± 8.8
Male, n (%)	49 (82.7)
Race/Ethnicity, n (%)	
African American	36 (60)
Caucasian	22 (36.7)
Other	2 (3.3)
Pre-treatment CD4 count, cells/mm^3, median (IQR)	210 (65–410)
Pre-treatment HIV RNA, copies/mL, median (IQR)	78,090 (23,900–227,800)
History of prior ARV exposure, n (%)	43 (71.7)
Concomitant nephrotoxic medications at TDF d/c, n (%)	30 (50)
Concomitant tubular secretion inhibitors at TDF d/c, n (%)	27 (45)
Duration of TDF exposure, months, median (IQR)	50.7 (25.6–68.8)
Time since HIV diagnosis, years, median (IQR)	10.8 (4.4–14.7)
ARV at the time of TDF d/c, n (%)	
NNRTI	17 (28.3)
PI	36 (60)
INSTI	13 (21.7)

Table 2. Renal function pre-TDF, at TDF d/c, and after TDF d/c

Time-frame (n=60)	SCr (mg/dL)	CG (mL/min)	MDRD (mL/min/m^2)
Pre-TDF, median (IQR)	1.1 (0.9–1.3)	71.8 (62.8–96.2)	78.3 (72.5–95.4)
At TDF d/c, median (IQR)	1.6 (1.5–1.8)	52.5 (43–59.8)	51.7 (45.9–60.6)
After TDF d/c, median (IQR)	1.2 (1.1–1.4)*	68 (54.8–83.6)*	73.5 (62.8–87.4)*

*p<0.001 versus at TDF d/c

Figure 1. MDRD eGFR throughout study period

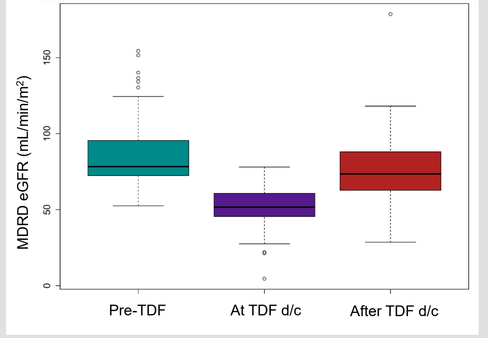

Table 3. Renal outcomes

Renal Outcome	Result
Time to improvement (n=48), months, median	5.4
Change in MDRD eGFR if improved (n=48), mL/min/m^2, median (IQR)	+21.6 (16.6–36.8)
Time to recovery (n=24), months, median	52.6
Change in MDRD eGFR if recovered (n=24), mL/min/m^2, median (IQR)	+27.9 (18–41.3)

- 48 (80%) patients satisfied criteria for *improvement*
- 24 (40%) patients satisfied criteria for *recovery*

Table 4. Factors associated with patients achieving recovery (n=24)

Variable	Univariate	Multivariate
	HR (95% CI);*p*-value	HR (95% CI);*p*-value
Male	6.8 (0.92, 50);0.061	4.5 (0.6, 34);0.14
Pre-treatment HIV RNA (log)	0.7 (0.4, 1.2);0.21	--
Pre-treatment CD4 (per every 100 cells/mm^3)	1.1 (0.95, 1.3);0.21	--
Receipt of thiazide diuretic at TDF d/c	1.8 (0.79, 4.1);0.16	--
Receipt of thiazide diuretic at time of recovery	3.1 (1.4, 7.1);0.007	3.2 (1.3, 7.6);0.01
Number of prior ARV regimens	1.3 (1.04, 1.7);0.025	1.4 (0.76, 2.5);0.29
Number of prior ARVs	1.2 (1.01, 1.3);0.032	0.97 (0.69, 1.4);0.88

Conclusions

- Among patients with suspected TAN, renal function improves for most patients after TDF d/c, but not all patients have complete recovery to baseline
- A patient's greatest improvement in renal function may not occur until many months after TDF d/c

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/Adult andAdolescentGL.pdf. Section accessed 2015 Nov 8.
2. Cooper RD, Wiebe N, Smith N, et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis. 2010 Sep 1;51(5):496-505.
3. Wever K, van Agtmael MA, Carr A. Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men. J Acquir Immune Defic Syndr. 2010 Sep 1;55(1):78-81.

Authors' Disclosures: Nothing to disclose