A Chronic Kidney Disease Risk Score to Determine Tenofovir Safety in a Prospective Cohort of HIV+ Male Veterans

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Background

- HIV-infected persons are at increased risk for chronic kidney disease (CKD) and end stage renal disease relative to persons without HIV infection.
- Tenofovir disoproxil fumarate (TDF) is a widely used antiretroviral for HIV infection that is part of first-line therapy and is associated with increased risk of CKD.
- However, relative risks are not completely informative, and there is a need for individualized decision making.
- Study objectives:
  - To derive a scoring system to predict 5-year risk of developing CKD
  - To estimate differences in risk associated with using tenofovir

Methods

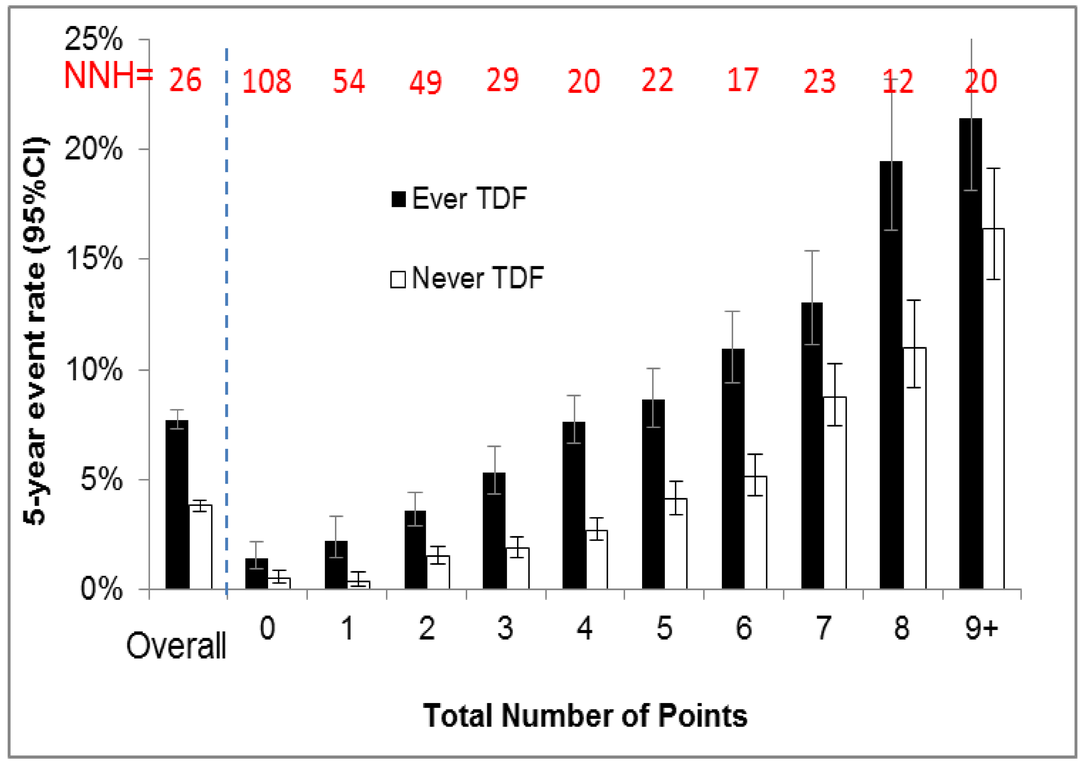
- **Setting**: Veterans Health Administration System (VHA)
- **Inclusion criteria:**
  - HIV-infected , new users of antiretroviral (ARV) therapy
- **Exclusion criteria:**
  - Kidney failure
  - Absent lab values
  - Baseline CKD
- **Sample size:** 21,590 HIV-infected men
- **Timeframe**: 1997 – 2010
- **Outcome**: Time to first occurrence of CKD (eGFR<60)
- Median follow-up was 6.3 years, during which 2,059 CKD events occurred.
- **Design**: Longitudinal cohort study
- Cox proportional hazards models to develop risk score:
  - Assessed traditional kidney risk factors and HIV-related factors for CKD, using stepwise backward selection (significance level of α=0.05) to remove candidate covariates.
  - Calculated points associated with each risk factor
  - Determined the 5-year probability of developing CKD associated with total number of points
  - Calculated point total for each participant using this risk score

Example of risk calculation: 55-year old HIV+ male with normal glucose, hypertension, hypertriglyceridemia, no proteinuria, and normal CD4 cell count:

Risk factor	Points
Age 55	4
Glucose>140 mg/dL	0
SBP>140 mmHg	1
Hypertension	2
TG>200 mg/dL	1
No proteinuria	0
CD4>200 cells/mm^3	0
Total Score	8
Estimated five year risk of CKD:	
If patient is put on tenofovir:	19% chance of developing CKD
If patient is not put on tenofovir:	11% chance of developing CKD

Results

Figure 1: Progressive increase in 5-year Risk of CKD in TDF ever and never users



- The overall 5-year event rate was 7.7% in tenofovir users and 3.8% in non-users (adjusted HR=2.0, 95%CI: 1.8-2.2). (Figure 1)
- We observed a progressive increase in the risk of CKD with increasing number of points from the risk score, with 5-year risks in non-users of tenofovir ranging from <1% in those with zero points to 16.4% in those with 9 or more points, and from 1.4% to 21.4% among tenofovir users.
- The overall number-needed-to-harm (NNH) for tenofovir use was 26, meaning that if 26 patients are exposed to TDF for 5 years, 1 would develop CKD that would not have otherwise.
- NNH for tenofovir use ranged from 108 for those with zero points to 20 for persons with 9 or more points.

Table 1: Baseline characteristics by end-of-study TDF use

Risk Factor	TDF exposure (n = 14,687)	No TDF exposure (n = 6,903)
Age (years)*	47 (40, 53)	48 (42, 54)
Black	52%	56%
Glucose (mg/dL)	95 (87, 106)	96 (87, 109)
Diabetic	5.4%	7.0%
Systolic BP (mmHg)	127 (116, 138)	128 (115, 140)
Diastolic BP (mmHg)	77 (70, 85)	77 (70, 85)
Hypertension	27%	28%
Proteinuria	23%	23%
HDL Cholesterol (mg/dL)	38 (30, 47)	39 (31, 49)
LDL Cholesterol (mg/dL)	100 (78, 125)	101 (76, 129)
Triglycerides (mg/dL)	138 (94, 216)	144 (98, 223)
CVD	3.9%	4.9%
Current Smoking	21%	17%
BMI (kg/m^2)	25 (22, 28)	24 (22, 27)
HIV Viral Load, (/1000)	14 (0, 92)	10 (0, 93)
CD4+ Count, (cells/mm^3)	314 (160, 492)	310 (143, 526)
Hepatitis C Virus Infection	23%	28%
*Continuous variables reported as median (IQR).		

Table 2: Factors associated with risk of CKD

Risk factor	Category	Hazard Ratio (95%CI)	Raw regression coefficient	Points
Age (per year)	19-39	1.06 (1.05, 1.07)	0.0619 = β_1	0
	40-49			2
	50-59			4
	60-90			6
Glucose > 140 mg/dL	No	1.60 (1.41, 1.82)	0.4719 = β_2	0
	Yes			2
SBP > 140 mmHg	No	1.23 (1.11, 1.35)	0.2049 = β_3	0
	Yes			1
Hypertension	No	1.76 (1.61, 1.92)	0.5632 = β_4	0
	Yes			2
TG > 200 mg/dL	No	1.31 (1.19, 1.44)	0.2696 = β_5	0
	Yes			1
Proteinuria	No	1.99 (1.77, 2.23)	0.6871 = β_6	0
	Yes			2
CD4<200 cells/mm^3	No	1.18 (1.07, 1.31)	0.1692 = β_7	0
	Yes			1

- Older age, elevated glucose (>140 mg/dL), elevated SBP (>140 mmHg), hypertension, elevated TG (>200 mg/dL), proteinuria, and low CD4 cell count were independently associated with a higher risk of developing CKD (Table 2).

Conclusions

- In this national sample of 21,590 male HIV-infected veterans, risk of CKD increased progressively with increasing number of points from the risk score.
- TDF users had a higher absolute risk of developing CKD compared with never users in those with both a lower and higher burden of comorbidities typically associated with renal dysfunction.
- The CKD risk score can be used to predict the absolute five-year risk of developing CKD for individual HIV-infected men.
- The availability of this information should guide clinicians and individual patients who are weighing the benefits of using tenofovir against the long term risks of kidney damage.

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