

Impact of Drug Therapy and Co-Morbidities on the Development of Renal Impairment in HIV-Infected Patients: Results of a Large Retrospective Database Study

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Background

- Both HIV and its treatment are documented to increase nephrotoxicity risk in HIV+ patients.¹⁻⁶
- While some studies have suggested ART-associated renal failure with tenofovir disoproxil fumarate (TDF), few have looked at this in African-American HIV+ patients.^{7,12}
- Most studies to date have used the Cockcroft-Gault (CG) method of calculating GFR, which may be more inaccurate than the Modification of Diet in Renal Disease (MDRD) method, which factors in body-surface area and has an adjustment factor for African-American race.
- The susceptibility of any antiretroviral treatment in the development of renal function decline must factor in all co-morbidities and non-HIV-related drug therapies patients are receiving.
- The purpose of this retrospective database study is to compare the relative frequency of renal impairment, as defined as CG- and MDRD-calculated GFR reduction >25% from baseline (BL), and time from treatment initiation until appearance of renal impairment. The effect of demographics, HIV disease characteristics, and co-morbidities on renal impairment rates were also assessed.

Methods

Study Design

- Phase IV retrospective, single-center, electronic database study
- Review of medical records of 691 HIV+ pts treated at the AIDS Arms Peabody Health Clinic (Dallas, TX) and followed for up to 4 yrs (2003-2006)
- Analysis of data from only HAART-treated patients monitored continuously at the center for ≥1 year
- Comparison of disease/Tx characteristics of pts whose GFR decreased >25% from BL with those with no GFR A
- GFR evaluated by both MDRD and Cockcroft-Gault (CG) methods

Data Collected

- Demographics, including age, gender, race/ethnicity, wt
- Labs, including VL, CD4 ct, serum creatinine
- Co-morbidities (HTN, DM, Hep C, Hep B)
- HAART drugs received, with start, stop, and A dates
- Non-HAART drugs received, with start, stop, and A dates
- Medication adherence via prescription refill records

Study Endpoints

- Time from study BL-to-event (GFR ↓ >25% from BL) in TDF-txtd vs non-TDF-txtd pts
- No. of pts who converted from NKF-defined mild to mod renal impmt (GFR 60-89 to 30-59 mL/min), or from mod to severe renal impmt (GFR 30-59 to 15-29 mL/min)
- Effect of co-morbidities on time to GFR ↓ >25% from BL

Statistical Analyses

- In HAART-treated patients monitored continuously at the center for ≥1 year, proportional hazards models were used to investigate an association of calculated GFR decrease >25% from BL ("renal impairment") with the following:
 - demographic and baseline variables;
 - use of different antiretroviral agents;
 - certain co-morbidities (hypertension, diabetes mellitus, hepatitis C infection, hepatitis B infection);
 - time on ART; and
 - time over which patients were monitored at the clinic (time-on-study).
- Significant covariates were selected into the model using the stepwise selection method

Patient Characteristics

- 323 patients treated for ≥1yr were available for evaluation (see tables)
- Most of the patients were males (82%) and black (61%)
- Mean age was 37.9y; mean weight was 75.4 kg
- About one-third were HCV+ (34%) and 6% were HBV+
- 29% were hypertensive and 3% diabetic
- 52% had been TDF-treated and 48% non-TDF-treated
- Mean BL MDRD-calculated GFR was 114.5 mL/min/1.73m²; and mean CG-calculated GFR was 120.6 mL/min/1.73m²
- Mean time-on-study was 979.9d (2.7y)

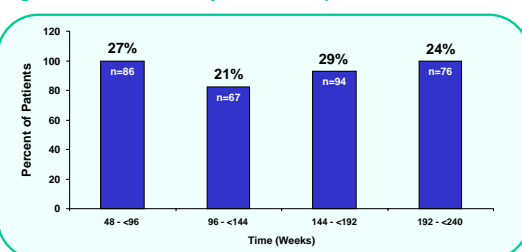
Results

Table 1. BL Characteristics of ART-Exposed Patients with ≥1 Year on Study

Sex	n	Female	Male	Total
		59 (18%)	264 (82%)	323
Age (y)	n			323
	Mean			37.9
	SD			8.5
Race	n			323
	Black	198 (61%)		
	White	62 (19%)		
	Hispanic	40 (12%)		
	Other	23 (8%)		
Weight (kg)	n			320
	Mean	75.4		
	SD	15.4		
Hepatitis B status	Negative	304 (94%)		
	Positive	19 (5%)		
Hepatitis C status	Negative	212 (66%)		
	Positive	111 (34%)		
Hypertension	No	229 (71%)		
	Yes	94 (29%)		
Diabetes	No	312 (97%)		
	Yes	11 (3%)		
Cockcroft-Gault GFR category (mL/min)	<30	1 (<1%)		
	30-60	5 (2%)		
	60-90	41 (13%)		
	≥90	230 (71%)		
	Missing	46 (14%)		
	Mean*	120.6		
	SD	41.2		
MDRD GFR category (mL/min)	<30	1 (<1%)		
	30-60	2 (<1%)		
	60-90	45 (14%)		
	≥90	232 (72%)		
	Missing	43 (13%)		
	Mean†	114.5		
	SD	36.7		

*n =277; †n =280

Figure 1. Time on Study for ART-Exposed patients



Discussion

- In this retrospective database study, no significant difference was observed between TDF-treated and non-TDF-treated pts in time from study BL to occurrence of a GFR ↓ by 25% below BL. Time-on-study, hypertension, weight, and age were the only significant predictors of GFR ↓ by 25% below BL.
- Tordato et al¹³ similarly reported in a comparable sized population (n=316), that older age, not type of HAART, was associated with reduced GFR. However, unlike our study, Tordato's study showed female gender and differences between nadir and current CD4 counts to be linked with GFR decrease.
- Over a mean 20-month follow-up period, Madeddu et al¹⁴ found in 354 TDF-treated HIV+ patients (67% men, mean age, 40 yrs, mean CD4+ ct 363 cells/mm³), that nephrotoxicity occurred more frequently in males and those who were HCV-coinfected, in CDC stage C, or with low CD4 counts. We did not see a relationship between HCV and GFR decrease.
- F. Wolf et al¹⁵ found over a median monitoring period of 22 months that 25% of 500 TDF-treated HIV+ patients developed mild renal impairment compared to 21% of 100 non-TDF-treated control patients. Many of the patients (41%) with reduced creatinine clearance while on TDF had pre-existing kidney impairment. Most (72%) of the TDF-treated patients were also taking other drugs that could potentially cause kidney toxicity, compared with just 12% in the TDF-sparing group.
- Our study was unique in that 61% of the data came from black HIV+ patients, a population at 12-fold higher risk for end-stage renal disease compared with the age- and race-adjusted national rate.¹⁶
- In summary, our study supports the idea that age, hypertension and weight are predictors of GFR ↓ by 25% below BL. Within a population that is at significant risk for renal impairment, antiretroviral therapy was not predictive. This may in part be related to the particular renal function endpoint we chose for assessment. Our study population had a relatively high mean BL GFR (≥114 mL/min), potentially lowering the risk for TDF-associated renal toxicity.¹⁵ Differences in our results from other studies also might have been attributable to between-study differences in rates of other types of co-morbidities or in types of co-administered drugs used by patients. Lastly, our study design had limitations that may have led to results that are different from those observed in other studies. First, we evaluated a relatively small population. And, second, our study did not have a randomized, controlled design in which patients were randomized to TDF- or non-TDF-containing arms and started on therapy at the same time.

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Table 2. BL Characteristics by TDF Status for ART-Exposed Patients ≥1 Yr on Study

	n	TDF+ (N=167)	TDF- (N=156)	Total (N=323)
Sex	n	167	156	323
	Female	38 (23%)	21 (13%)	59 (18%)
	Male	129 (77%)	135 (87%)	264 (82%)
Age (y)	n	167	156	323
	Mean	37.4	38.4	37.9
	SD	8.0	9.0	8.5
Race	n	167	156	323
	Black	96 (57%)	102 (65%)	198 (61%)
	White	41 (25%)	21 (13%)	62 (19%)
	Hispanic	19 (11%)	21 (13%)	40 (12%)
	Other	11 (7%)	12 (8%)	23 (8%)
Weight (kg)	n	165	155	320
	Mean	75.1	75.6	75.4
	SD	15.3	15.6	15.4
Hepatitis B status	Negative	154 (92%)	150 (96%)	304 (94%)
	Positive	13 (8%)	6 (4%)	19 (6%)
Hepatitis C status	Negative	110 (66%)	102 (65%)	212 (66%)
	Positive	57 (34%)	54 (35%)	111 (34%)
Hypertension	No	117 (70%)	112 (72%)	229 (71%)
	Yes	50 (30%)	44 (28%)	94 (29%)
Diabetes	No	166 (>99%)	146 (94%)	312 (97%)
	Yes	1 (<1%)	10 (6%)	11 (3%)
Cockcroft-Gault GFR category (mL/min)	<30	0	1 (<1%)	1 (<1%)
	30-60	2 (1%)	3 (2%)	5 (2%)
	60-90	25 (15%)	16 (10%)	41 (13%)
	≥90	115 (69%)	115 (74%)	230 (71%)
	Missing	25 (15%)	21 (13%)	46 (14%)
	Mean	120*	121.2†	120.6†
	SD	45.6	36.2	41.2
MDRD GFR category (mL/min)	<30	0	1 (<1%)	1 (<1%)
	30-60	1 (<1%)	1 (<1%)	2 (<1%)
	60-90	30 (18%)	15 (10%)	45 (14%)
	≥90	113 (68%)	119 (76%)	232 (72%)
	Missing	23 (14%)	20 (13%)	43 (13%)
	Mean	114†	115‡	114.5†
	SD	44.4	26.4	36.7

*n = 142; †n = 144; ‡n = 135; §n = 136; ¶n = 277; ††n = 280

Figure 2. Distribution of Time on Study in TDF-treated Patients (N=167)

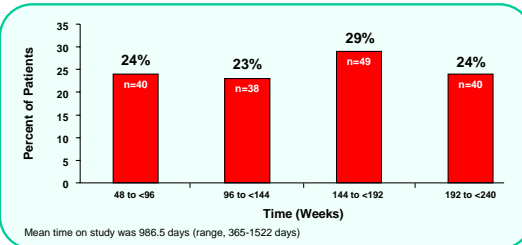
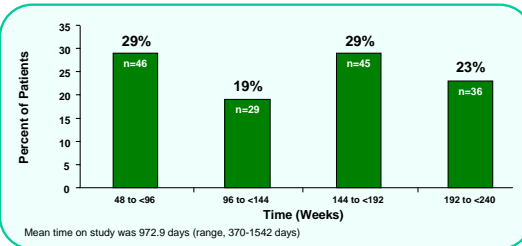


Figure 3. Distribution of Time on Study in Non-TDF-treated Patients (N=156)



- Using the CG GFR, age, weight, and time on study were found to significantly predict a >25% decline from BL in GFR (Table 4)
 - For each year increase in age at BL, the hazard of having >25% decline from BL in CG GFR increases by 3.9%
 - For each unit increase in weight, the hazard of having >25% decline from BL in CG GFR decreases by 1%
 - For each additional day in the study, the hazard of having >25% decline from BL in CG GFR decreases by 0.1%

Table 3. Summary of Proportional Hazards Model for Cockcroft-Gault GFR Using Stepwise Selection Method (ART-Exposed for ≥1 Yr)

Variable (N=162)	Parameter Estimate (sd)	p-value	Hazard Ratio
Cockcroft-Gault (CG) GFR	0.0136 (0.0019)	<0.0001	1.014
Age (y)	0.0381 (0.0143)	<0.0077	1.039
Weight (lbs)	-0.0128 (0.0042)	0.0023	0.987
Time on Study (days)	-0.0013 (0.0004)	0.0043	0.999

- Using the MDRD GFR, time on study and hypertension status at BL significantly predict a >25% decline from BL in GFR (Table 5)
 - For each additional day in the study, the hazard of having >25% decline from BL in MDRD GFR decreases by 0.1% (similar results as in the CG GFR)
 - Patients with hypertension at BL are 1.7 times more likely to have >25% decline from BL in MDRD GFR than those who were not hypertensive at BL

Table 4. Summary of Proportional Hazards Model for MDRD GFR Using Stepwise Selection Method (ART-Exposed for ≥1 Yr)

Variable (N=162)	Parameter Estimate (sd)	p-value	Hazard Ratio
Modified GFR (eGFR)	0.0120 (0.0016)	<0.0001	1.012
Time on Study (days)	-0.0012 (0.0004)	0.0017	0.999
Hypertension	0.5342 (0.2213)	0.0158	1.706