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Renal function in patients with pre-existing renal disease receiving tenofovir-containing HAART in the HIV Outpatient Study (HOPS) cohort

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Abstract (updated)

Background: Sporadic cases of incident renal disease have been reported in HIV-infected patients with normal baseline renal function who received tenofovir (TDF), but little data exist on the safety of TDF in patients with pre-existing renal dysfunction. We characterized renal profiles in such patients who received TDF-containing HAART in the HOPS, an open longitudinal cohort of patients seen at 10 U.S. clinics.

Methods: HOPS patients who initiated and received >1 month of TDF after November 1, 2001 were considered for analyses. We identified two subsets of patients: (i) persons with a prior diagnosis of renal insufficiency but having baseline creatinine < 1.5 mg/dL and CrCl > 50 mL/min ('past renal dysfunction'), and (ii) persons with baseline creatinine ≥ 1.5 mg/dL and/or CrCl < 50 mL/min, and at least one prior creatinine ≥ 1.5 mg/dL ('current renal dysfunction'). We examined 12-month changes in CrCl estimated by Cockcroft-Gault equation, glomerular filtration rate (GFR) estimated by simplified Modification of Diet in Renal Disease (MDRD) equation, and staged GFR by National Kidney Foundation (NKF) criteria.

Results: Nineteen TDF-exposed persons (baseline values: 79% male, median age 48 years, median CD4 cell count 322 cells/μL, median 10.1 years since HIV diagnosis, all antiretroviral experienced) met inclusion criteria. They were followed a median of 13 months (range 6-35) with a median of 5 (range 2-16) creatinine determinations. At baseline, median creatinine was 1.7 mg/dL, CrCl 56 mL/min, GFR 49 mL/min/1.73m^2. Past or current diagnoses included hypertension (9 persons, 48%) and diabetes (2 persons, 11%). Most received TDF 300 mg once daily; 2 persons received TDF 300 mg 3 times weekly. Among 6 persons with past renal dysfunction, 3 had an increase in NKF stage (at least two consecutive higher values) in follow-up. Among 13 subjects with current renal dysfunction, 2 had an increase in NKF stage in follow-up. Among 10 subjects with current renal dysfunction who had 12-month data, the mean 12-month change in CrCl was +2.9 mL/min (median +4.6, range: -24.0 to +23.7) and the mean 12-month change in GFR was +3.7 mL/min/1.73 m^2 (median +7.5; range: -24.3 to + 29.5) (signed rank test for changes, P>0.05 for all).

Conclusions: In this case series of HIV-infected persons with past or active renal dysfunction, a small number had reductions in CrCl or GFR over a median follow-up of 13 months on TDF-containing HAART.

Introduction

- Tenofovir disoproxil fumarate (TDF), has been demonstrated to be safe and generally well tolerated for treatment of HIV-1 infection, and has not been associated with significant renal toxicity in randomized placebo-controlled clinical trials (RTC) of patients with normal baseline renal function (1-5)
- However, cases of severe renal dysfunction (6-8) and population-level reductions in creatinine clearance among TDF-treated patients have been reported in observational studies post-licensure (9-13)
- Few analogous data exist for patients with pre-existing renal dysfunction taking TDF-containing HAART (8, 14).

Objective

- To examine renal profiles among HIV-infected patients with pre-existing renal dysfunction who received TDF-containing HAART in the HIV Outpatient Study

Methods

HIV Outpatient Study (HOPS)

- HOPS is a prospective cohort study of HIV-infected patients seen at 10 clinics (public and private) specializing in treatment of HIV disease in seven cities in the United States. HOPS has collected sociodemographic and clinical data abstracted from medical charts on about 8,000 patients from 1993 to date

Study design and population

- A case series of 19 antiretroviral-experienced patients enrolled in the HOPS who received >1 month of TDF-containing HAART after November 1, 2001.
- Observation time began at baseline, defined as the start date of first TDF-containing HAART. It was censored at 36 months after baseline, at the time patient discontinued TDF-containing HAART, or at death, loss to follow-up, or September 30, 2005

Inclusion criteria

- Had serum creatinine measured at least once within 6 months prior to starting TDF-HAART and at least twice more during follow-up
- Met criteria for one of the following two subgroups:
  (i) Prior diagnosis of renal insufficiency but baseline creatinine < 1.5 mg/dL and CrCl > 50 mL/min ('past renal dysfunction')
  (ii) Baseline creatinine ≥ 1.5 mg/dL and/or CrCl < 50 mL/min, and at least one prior creatinine ≥ 1.5 mg/dL ('current renal dysfunction').

Exclusion criteria

- Prior or concurrent exposure to adefovir or cidofovir
- Concurrent pregnancy
- Dialysis

Definitions and equations

Estimated Creatinine Clearance (CrCl, mL/min) by Cockcroft-Gault (CG) equation (15)†

= [((140 – age [yrs]) * weight [kg]) / (serum creatinine [mg/dL] * 72)] * (0.85 if female)

† CrCl by CG calculated using age and weight closest in time to the serum creatinine measurement (+/- 3 months)

Estimated Glomerular Filtration Rate (GFR, mL/min/1.73m^2) by the simplified Modification of Diet in Renal Disease (MDRD) equation (16)

= 186 * (creatinine [mg/dl]) $^{-1.154}$ * (age) $^{-0.203}$ * (0.742 if female) * (1.210 if African American)

National Kidney Foundation (NKF) classification system to stage renal disease by MDRD (mL/min/1.73m^2)

Stage 1: GFR ≥ 90
Stage 2: GFR 60-89
Stage 3: GFR 30-59
Stage 4: GFR 15-29
Stage 5: GFR < 15

Primary outcome

- Confirmed increase in NKF stage from baseline (2 or more consecutive GFR values meeting criteria for renal disease at any stage greater than baseline stage)

Statistical analyses

- Univariate changes in CrCl and GFR from baseline to 12 months (+/- 3 months) among those with both measurements

Results

Baseline characteristics (N = 19)

- 79% male
- Median age = 48 years
- Median CD4+ cell count = 322 cells/mm^3
- Median time since HIV diagnosis = 10.1 years
- Median creatinine = 1.7 mg/dL
  - CrCl 56 mL/min
  - GFR 49 mL/min/1.73m^2
- Renal dysfunction category:
  - Past renal insufficiency = 6 patients
  - Current renal insufficiency = 13 patients

Follow-up characteristics (N = 19)

- Median period of follow-up = 13 months (range 6 - 35)
- Median number of creatinine determinations = 5 (range 2 - 16)
- TDF dosing:
  - TDF 300 mg once daily for 17 patients
  - TDF 300 mg 3x weekly for 2 patients

Renal function in follow-up

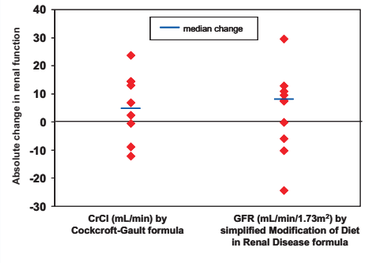
Confirmed increase in NKF stage during follow-up:

- 3 of 6 patients who had past renal dysfunction
- 2 of 13 patients with current renal dysfunction

12-month change in renal function from baseline:

- Among 15 of 19 of ALL patients:
  - Δ CrCl (mL/min): mean -0.8 (median -0.3, range -32.2 - +23.6)
  - Δ GFR (mL/min/1.73m^2): mean -1.3 (median -0.1, range -49.8 - +29.5)
- Among 10 of 13 patients categorized as 'CURRENT RENAL DYSFUNCTION':
  - Δ CrCl (mL/min): mean +2.9 (median +4.6, range -24.0 - +23.7)
  - Δ GFR (mL/min/1.73m^2): mean +3.7 (median +7.5, range -24.3 - +29.5)

Changes in renal function among ten patients categorized as having 'current renal dysfunction' with both baseline and 12-month values, HIV Outpatient Study, November 2001 – September 2005



Characteristics of 19 patients with renal dysfunction prior to initiating TDF-containing HAART, HIV Outpatient Study, November 2001 - September 2005

ID	Age	Sex	Race	Contributing Conditions	Nadir CD4+ count	Baseline CD4+ count	History of renal disease	Baseline creatinine (mg/dL)	Baseline CrCl (mL/min)	Baseline GFR (mL/min/ 1.73m^2)	Baseline NKF stage	First TDF-containing HAART regimen	Period of follow-up (mos)	Number of creatinine determinations in follow-up	Lowest CrCl	Months to lowest CrCl	Lowest GFR	Lowest NKF stage	Months to lowest GFR
Past renal dysfunction																			
A	44	F	B	HCV	44	351	RI	1.3	68	57	3	TDF+3TC+EFV	22	2	63	2	52	3	3
B	51	M	W	HTN, HCV	80	180	RI	1.4	71	57	3	TDF+3TC+NVP	15	16	39	8	34	3	8
C	54	M	W	DM	180	1364	RI	1.1	165	74	2	TDF+3TC+SAQ+Rtvld	26	6	130	19	56	3	19
D	37	M	H	HTN	19	322	RI	1.3	71	66	2	TDF+3TC+ABC+NVP	34	9	48	<1	42	3*	<1
E	36	M	W		75	518	RI	1.3	92	66	2	TDF+ddI+EFV	33	12	67	30	48	3*	30
F	36	F	B	IDU	14	76	RI	0.7	90	122	1	TDF+AZT+SAQ+LPV/Rtvld	14	5	54	4	65	2*	4
Current renal dysfunction																			
G	61	F	B	HTN	346	346		1.8	37	37	3	TDF+AZT+3TC+FTC+EFV	11	11	12	11	10	5*	11
H	41	M	W	HTN	255	374	RI	2.5	43	30	3	TDF+ABC+APV+LPV/Rtvld	11	5	34	10	24	4*	10
I	69	F	W		144	144		1.4	34	40	3	TDF+FTC+EFV	12	8	26	1	30	4	1
J	48	M	B	DM, HCV	147	313		1.6	69	59	3	TDF+3TC+NVP	12	3	69	1	59	3	1
K	25	M	W		930	1044		1.8	72	49	3	TDF+3TC+ABC+NVP	13	4	85	13	60	3	13
L	59	M	B	HTN	6	6		1.8	40	50	3	TDF+AZT+3TC+DLV+LPV/Rtvld+T20	30	14	36	1	44	3	1
M	55	M	W	HTN	214	828		2.1	51	35	3	TDF+FTC+ATV+Rtvld	10	3	57	1	42	3	1
N	40	M	W		308	506		1.9	56	42	3	TDF+3TC+EFV	29	5	70	9	55	3	9
O	45	M	B	HTN	13	190	RI	2.2	48	42	3	TDF (3W)+ABC+LPV/Rtvld	6	2	40	6	36	3	6
P	76	M	W		56	137		1.6	35	45	3	TDF (3W)+ABC+ATV+Rtvld	12	6	28	8	37	3	8
R	38	M	B		120	167		1.7	61	58	3	TDF+ddI+LPV/Rtvld	11	5	46	2	45	3	2
S	52	M	W	HTN	26	464	RI**	2.3	43	32	3	TDF+ddI+EFV	35	11	44	5	37	3	26
T	62	M	W	HTN	101	322		1.7	44	44	3	TDF+NVP+LPV/Rtvld	7	2	58	3	59	3	3

* Reduction in NKF stage from baseline confirmed by one or more consecutive values
** Additional diagnoses included interstitial nephritis and glomerulonephritis

NOTE: RI = renal insufficiency, HTN = hypertension, DM = diabetes, HCV = hepatitis C coinfected, 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ATV = atazanavir, AZT = zidovudine, ddI = didanosine, DEL = delavirdine, EFV = efavirenz, FTC = emtricitabine, NVP = nevirapine, LPV = lopinavir, Rtvld = low-dose ritonavir, SQV = saquinavir, T20 = enfuvirtide, TDF = tenofovir

TDF dosing daily, unless otherwise specified

Limitations

- Small case series
- Analyzed routinely collected clinical data from HIV outpatients; no fixed schedule of creatinine measurements
- Diagnoses of renal disease were made by treating physicians; not standardized across the sites
- No routine urinalyses to describe the rates of glycosuria or protenuria

Conclusion

In this case series of HIV-infected patients with past or current renal dysfunction who received TDF-containing HAART (many of whom had other comorbidities), most patients did not experience a worsening of NKF stage during a median 13 months of follow-up.

Recommendation

For patients with pre-existing renal dysfunction who are prescribed TDF-containing HAART, close monitoring of renal function is warranted and dose adjustment of TDF may be indicated

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Appendix

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