Prevalence and Factors Associated with Renal Dysfunction Among HIV-Infected Patients

Nancy Crum-Cianflone, M.D., M.P.H.^{1,2} Anuradha Ganesan, M.D.^{2,3} Nimfa Teneza-Mora, M.D., M.P.H.¹ Mark Riddle, Ph.D.⁴ Sheila Medina, M.P.H.^{1,2} Irma Barahona^{2,3} and Stephanie Brodine, M.D.⁵

Abstract

Renal dysfunction is an increasingly recognized non-AIDS-defining comorbidity among HIV-infected persons. The role of HIV-related factors in renal dysfunction remains unclear. We performed a cross-sectional study at two military clinics with open access to care to determine the impact of HIV factors, including antiretroviral therapy, on renal function. Renal dysfunction was defined as a glomerular filtration rate (GFR) < 60 mL/min/ 1.73 m². We evaluated 717 HIV patients with a median age of 41 years; 92% were male, 49% Caucasian, and 38% African American; median CD4 count was 515 cells/mm³ and 73% were receiving highly active antiretroviral therapy (HAART). Twenty-two patients (3%) had renal dysfunction. Factors associated with renal dysfunction in the multivariate logistic analyses included older age (odds ratio [OR] 2.0 per 10 year increase, p = 0.006), lower CD4 nadir (OR 0.6 per 100 cell change, p = 0.02), and duration of tenofovir use (OR 1.5 per year use, p = 0.01). Among persons initiating tenofovir (n = 241), 50% experienced a reduction in GFR (median -10.5 mL/min/1.73 m², 95% CI, -8.9 to -13.3) within 2 years. Among tenofovir users, factors associated with a reduction in GFR included female gender (p < 0.001), African American ethnicity (p = 0.003), and lower CD4 nadir (p = 0.002). In summary, renal dysfunction was relatively uncommon among our HIV-infected patients, perhaps due to their young age, lack of comorbidities, or as a result of our definition that did not include proteinuria. Renal dysfunction was associated with duration of tenofovir use. Factors associated with renal loss among tenofovir users included female gender, African American ethnicity, and CD4 nadir <200 cells/mm³. Consideration for more frequent monitoring of kidney function among these select HIV patients may be warranted.

Introduction

CHRONIC KIDNEY DISEASE has become an important comorbidity among HIV-infected persons.¹ Since the introduction of highly active antiretroviral therapy (HAART), the number of deaths due to opportunistic infections has significantly declined, while a greater proportion of patients are developing chronic conditions not traditionally related to HIV, such as cardiovascular, liver, and kidney disease.^{2,3} As the prevalence of HIV infection increases as a result of improved survival, the prevalence of renal dysfunction is projected to increase.⁴

Chronic kidney disease during the pre-HAART period was largely a result of HIV-associated nephropathy (HIVAN), which was associated with African American ethnicity and low CD4 cell counts.^{5,6} The introduction of HAART has resulted in significant change in the epidemiology of renal disease among HIV patients, with a substantial reduction in the incidence of HIVAN.⁷ Even with the benefits of HAART, chronic kidney disease remains common among HIV patients. A recent study showed that despite HAART use, kidney function loss continued to occur among HIV-infected persons.⁸ Contributing factors to renal disease among HIV patients includes the aging of the population, concurrent medical conditions such as diabetes mellitus and hypertension, and uncontrolled viremia.^{8,9}

In addition, certain antiretroviral medications may contribute to loss of renal function. Some studies have linked tenofovir with renal insufficiency, while others have not shown this finding.¹⁰⁻¹⁹ The purpose of this study was to

¹HIV Clinic, Naval Medical Center San Diego, San Diego, California.

²Infectious Disease Clinical Research Program (IDCRP), Uniformed Services University of the Health Sciences, Bethesda Maryland.

³Infectious Disease Clinic, National Naval Medical Center, Bethesda, Maryland.

⁴Naval Medical Research Center, Rockville, Maryland.

⁵Graduate School of Public Health, San Diego State University, San Diego, California.

Report Docume	Form Approved OMB No. 0704-0188			
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlin VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information does not display a currently valid OMB control number.				
1. REPORT DATE 2010	2. REPORT TYPE	3. DATES COVERED 00-00-2010 to 00-00-2010		
4. TITLE AND SUBTITLE		5a. CONTRACT NUMBER		
Prevalence and Factors Associated wit	5b. GRANT NUMBER			
HIV-Infected Patients	5c. PROGRAM ELEMENT NUMBER			
6. AUTHOR(S)	5d. PROJECT NUMBER			
	5e. TASK NUMBER			
	5f. WORK UNIT NUMBER			
7. PERFORMING ORGANIZATION NAME(S) AND AI Naval Medical Center San Diego,1HIV	8. PERFORMING ORGANIZATION REPORT NUMBER			
9. SPONSORING/MONITORING AGENCY NAME(S) A	10. SPONSOR/MONITOR'S ACRONYM(S)			
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribut	on unlimited			
13. SUPPLEMENTARY NOTES				
^{14. ABSTRACT} Renal dysfunction is an increasingly represented for the second second	rs in renal dysfunction remains uncle inics with open access to care to dete	ear. We performed a rmine the impact of HIV		

factors, including antiretroviral therapi, on renal function. Renal dysfunction was defined as a glomerular filtration rate (GFR) < 60 mL/min/ 1.73 m . We evaluated 717 HIV patients with a median age of 41 years; 92% were male, 49% Caucasian, and 38% African American; median CD4 count was 515cells/mm3 and 73% were receiving highly active antiretroviral therapy (HAART). Twenty-two patients (3%) had renal dysfunction. Factors associated with renal dysfunction in the multivariate logistic analyses included older age (odds ratio [OR] 2.0 per 10 year increase, p = 0.006), lower CD4 nadir (OR 0.6 per 100 cell change, p = 0.02), and duration of tenofovir use (OR 1.5 per year use, p = 0.01). Amony persons initiating tenofovir (n = 241), 50% experienced a reduction in GFR (median -10.5mL/min/ 1.73 m , 95% CI, -8.9 to -13.3) within 2 years. Among tenofovir users, factors associated with a reduction in GFR included female gender (p < 0.001), African American ethnicity (p = 0.003), and lower CD4 nadir (p = 0.002). In summary, renal dysfunction was relatively uncommon among our HIV-infected patients, perhaps due to their young age, lack of comorbidities, or as a result of our definition that did not include proteinuria. Renal dysfunction was associated with duration of tenofovir use. Factors associated with renal loss among tenofovir users included female gender, African American ethnicity, and CD4 nadir <200cells/mm3 . Consideration for more frequent monitoring of kidney function among these select HIV patients may be warranted.

16. SECURITY CLASSIFIC	17. LIMITATION OF	18. NUMBER	19a. NAME OF		
	ABSTRACT	OF PAGES	RESPONSIBLE PERSON		
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified	Same as Report (SAR)	9	

Standard Form 298 (Rev. 8-98) Prescribed by ANSI Std Z39-18 determine the prevalence and factors, including the impact of tenofovir, associated with renal dysfunction among a population of HIV-infected patients seen at two military clinics during the HAART era.

Methods

A cross-sectional retrospective study of HIV-infected patients was conducted at Naval Medical Center San Diego (NMCSD) and National Naval Medical Center (NNMC) HIV clinics from June 1, 2004 through June 30, 2005. The study was approved by the Institutional Review Boards at NMCSD, NNMC, and San Diego State University. The patient population consisted of Department of Defense beneficiaries, all of whom had free access to health care and medications. Active duty military members are initially HIV-negative upon entry into military service and undergo periodic HIV testing approximately every 2 years. Hence, the majority (n = 518, 72%) of our study participants had documented dates of seroconversion allowing for accurate determination of duration of HIV infection.

Data were abstracted from the medical records of 717 active patients, 371 at NMCSD and 341 at NNMC. Data obtained from the medical records included current age, gender, ethnicity, duration of HIV infection, presence of concurrent medical conditions (hypertension, diabetes mellitus, chronic hepatitis B, and chronic hepatitis C), serum creatinine, current CD4 cell count, nadir CD4 cell count, and current HIV RNA viral load. All antiretroviral medications were recorded, including the use of tenofovir, didanosine, and protease inhibitors. Creatinine levels were determined at each of the two participating sites' laboratories, which are Clinical Laboratory Improvement Amendments (CLIA) certified. A calibration of the levels for comparability was performed to adjust between creatinine measures at the two sites.

Hypertension was defined as a blood pressure greater than 140/90 mm Hg on at least two of any three prior clinic visits, by a physician diagnosis, or the use of an antihypertensive medication. Diabetes mellitus was defined by physician diagnosis or receipt of an antidiabetic agent. Chronic hepatitis B was defined as a positive surface antigen test (HBsAg), and chronic hepatitis C as a positive antibody test or detectable hepatitis C viral load. CD4 cell counts were examined as both continuous variables as well as categorically using clinically relevant cut-points. HIV RNA was log₁₀ transformed and was also categorized as undetectable (<50 copies per milliliter).

The estimated glomerular filtration rate (eGFR) was calculated using the four variable Modification of Diet in Renal Disease (MDRD) equation²⁰ and defined for our primary analysis as no renal dysfunction (eGFR \geq 60 mL/min/ 1.73 m²) or renal dysfunction (eGFR < 60 mL/min/1.73 m²). Of note, we utilized a single measurement for determination of renal dysfunction rather than measurements over a 3-month or greater period used to establish chronic kidney disease.²¹ For descriptive purposes, renal function was further categorized as less than 90, less than 60, or less than 30 mL/ min/1.73 m² based on the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline.²¹

Given the *a priori* defined objective to evaluate the effect of tenofovir on renal dysfunction, additional analyses were

conducted evaluating HIV patients initiating tenofovir. We collected information on the eGFR during the 2 years prior to tenofovir initiation and during the 2 years after, including only patients with at least two values during each time period. An overall mean change in eGFR was calculated. Similar data were collected on those initiating HAART without tenofovir. Some subjects were excluded from these analyses due to unavailability of creatinine values during both time periods (some participants began tenofovir or HAART at another medical clinic or had discontinued its use prior to adequate follow-up creatinine values) or because of recent initiation of therapy.

Statistical analysis included descriptive, univariate, and multivariate analyses. For the dichotomous outcome of renal dysfunction, each risk factor was evaluated using Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Variables significantly associated with renal dysfunction in univariate analyses (p < 0.10) were included in a multivariate logistic regression model utilizing a stepwise backward elimination to determine the influence and adjust for confounding among factors of interest and renal dysfunction. The secondary outcome of change in eGFR after tenofovir initiation was similarly evaluated for an association with prospective risk factors using univariate and multivariate linear regression models. Differences in median changes in eGFR between tenofovir and nontenofovir regimens were assessed using Wilcoxon rank sum testing. A p value of less than 0.05 was considered significant. Analyses were performed using Stata Version 10.0 (StataCorp, College Station, TX).

Results

Of the 717 study participants, the median age was 41 (interquartile range [IQR] 36–6) years, 92% were male, 49% were Caucasian, 38% were African American; 13% were other races (Table 1). Thirty-three percent had hypertension and 8% diabetes mellitus. The median duration of HIV infection was 12 years (IQR 6–17), and the median current CD4 cell count was 515 cells/mm³ (IQR 370–706) with HIV RNA viral load being undetectable (<50 copies per milliliter) in 43% of the study population. Of the study cohort, 73% of the subjects were receiving HAART; the regimen included tenofovir in 44% of cases with a median duration of use of 1.9 (IQR 1–2.8) years.

Among the study cohort, 258 patients (36%) had an eGFR < 90 mL/min/1.73 m². The prevalence of an eGFR of <60 mL/min/1.73 m² was 3% (n = 22). Of those with an eGFR of <60, 2 (0.2%) patients had an eGFR of <30 and no patient had an eGFR of <15 mL/min/1.73 m². Among subjects with eGFR < 60 mL/min/1.73 m², 59% (n = 13) were receiving tenofovir; of these, the median duration of use was 2.8 (IQR 2.1–4.0) years.

The factors associated with renal dysfunction (defined as an eGFR < 60 mL/min/1.73 m²) in the univariate models are summarized in Table 1. HIV patients with renal dysfunction were more likely to be older (OR 2.7 per 10 year increase in age, p < 0.001), have diabetes (OR 3.6, p = 0.02), have hypertension (OR 3.8, p = 0.003), have a longer duration of HIV infection (OR 1.1 per year, p = 0.007), and a lower CD4 nadir (OR 9.4 for CD4 <200 compared to \geq 200 cells/mm³, p < 0.001). Higher current CD4 counts (OR 0.8 per 100 cell increase, p = 0.01) were associated with a lower occurrence of

RENAL DYSFUNCTION IN HIV PATIENTS

TABLE 1.	FACTORS .	Associated	with Renal	IMPAIRMENT	AMONG H	HIV-INFECTED	Patients
----------	-----------	------------	-------------------	------------	---------	--------------	----------

Factora	<i>Total</i> n = 717	Normal renal function n = 695	Renal dysfunction ^b n = 22	OR	95% CI	p Value
Demographics						
Age, per 10 years	41 (36–46)	41 (35–46)	48 (41–62)	2.73	1.79–4.17	<0.001
Gender, male	662 (92.3)	642 (97.0)	20 (90.9)	1.21	0.27-5.32	0.80
Ethnicity ^c						
Caucasian	349 (48.7)	336 (48.4)	13 (59.1)	1.0		
African American	271 (37.9)	264 (38.0)	7 (31.8)	0.69	0.27–1.74	0.43
Other	96 (13.4)	94 (13.5)	2 (9.1)	0.74	0.35-1.57	0.44
Site						
San Diego	371 (51.7)	355 (51.1)	16 (72.7)	1.0		
Bethesda	346 (48.3)	340 (48.9	6 (27.3)	0.39	0.15-1.01	0.05
Concurrent medical conditions and	laboratory valu	es				
Diabetes	57 (8)	52 (7.5)	5 (22.7)	3.63	1.28-10.2	0.02
Hypertension	234 (32.6)	220 (31.7)	14 (63.6)	3.77	1.56-9.14	0.003
Chronic hepatitis B	37 (5.2)	37 (5.3)	0 (0)	_		_
Chronic hepatitis C	28 (3.9)	27 (3.9)	1 (4.6)	1.17	0.15–9.07	0.88
Trimethoprim-sulfamethaxazole use	60 (8.4)	56 (8.1)	4 (18.2)	2.54	0.83–7.75	0.10
Triglycerides	• •					
Per 30 mg/dL increase	149 (98–227)	149 (98–224)	134 (102–302)	1.01	0. 94– 1.10	0.75
>150 mg/dL	358 (49.9)	348 (50.1)	10 (45.5)	0.83	0.35-1.95	0.67
Total cholesterol						
Per 30 mg/dL increase	183 (156-208)	183 (156-207)	196 (156–223)	1.01	0.91–1.13	0.81
>200 mg/dL	225 (31.4)	216 (31.1)	9 (40.9)	1.53	0.65-3.64	0.33
LDL	. ,	• •				
Per 30 mg/dL increase	107 (86-129)	106 (86-128)	113 (92–134)	1.22	0.83-1.78	0.31
>130 mg/dL	175 (24.4)	167 (24)	8 (36.4)	1.81	0.74-4.38	0.19
HDL						
Per 10 mg/dL increase	38 (32-46)	38 (32-46)	39 (33–47)	0.92	0.66–1.29	0.63
<35 mg/dL	253 (35.3)	245 (35.3)	8 (36.4)	1.05	0.43-2.53	0.91
HIV-related factors						
Duration of HIV infection, years	11.5 (6–16.5)	11.5 (6–16)	16.5 (12–18)	1.13	1.03-1.24	0.007
CD4 Nadir per 100 cells	11.0 (0 10.0)	11.0 (0 10)	1010 (12 10)			
Median (IQR)	267 (149-370)	270 (156–372)	90 (13–153)	0.49	0.33-0.71	< 0.001
<200	243 (33.9)	225 (32.4)	18 (81.8)	9.40	3.14-28.10	< 0.001
>200	474 (66.1)	470 (67.6)	4 (18.2)	1.00		
Current CD4 per 100 cells	., . (00.1)	1,0 (0,10)	- (/			
Median (IQR)	515 (370–706)	520 (373-708)	391 (237-499)	0.77	0.64-0.94	0.01
<350	154 (21.5)	145 (20.9)	9 (40.9)	1.00		
350-500	189 (26.3)	181 (26.0)	8 (36.4)	0.71	0.27-1.89	0.50
>500	374 (52.2)	369 (53.1)	5 (22.7)	0.47		0.007
Log ₁₀ HIV RNA	2.1 (1.7-3.5)	2.1 (1.7–3.5)	2.4 (1.7–3.8)	-	0.78-1.62	0.54
HIV RNA <50 copies/mL	308 (43.0)	298 (42.9)	10 (45.5)	1.11		0.82
Current HAART, y/n	520 (72.5)	501 (72.1)	19 (86.4)		0.72-8.38	0.15
Current tenofovir	318 (44.4)	305 (43.9)	13 (59.1)		0.78-4.38	0.16
Duration of use per year ^d	1.9 (1-2.8)	0.96 (0.92–2.8)	2.8 (2.1-4.0)		1.47-2.69	0.003
Tenofovir with protease inhibitor	192 (26.8)	182 (26.2)	10 (45.5)	2.34		0.05
Lenotovir with protease indicator						

^aFactor expressed as number (percentage) for categorical variables and as median (interquartile range) for continuous variables. ^bRenal impairment defined as an estimated glomerular filtration rate of <60 mL/min/1.73m² by the MDRD equation.

'Ethnicity was missing for one participant.

^dAmong those receiving tenofovir.

OR, odds ratio; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IQR, interquartile range; HAART, highly active antiretroviral therapy; MDRD, Modification of Diet in Renal Disease.

renal dysfunction. We examined the HIV RNA level in terms of an undetectable level and as a continuous variable (log_{10} transformed) and found no significant association with renal dysfunction. The clinical site had a borderline significant relationship with renal dysfunction (p = 0.05).

dysfunction (OR 1.8, p = 0.16), but the duration of tenofovir use was associated (OR 2.0 per year of use, p = 0.003). We examined the combination of tenofovir with a protease inhibitor and found a marginal association (OR 2.3, p = 0.05).

We examined the effect of antiretroviral medications on renal dysfunction. In univariate analyses (Table 1), current receipt of tenofovir was not significantly associated with renal The two multivariate logistic regression models were built (one model with tenofovir alone and one with tenofovir plus protease inhibitor) and included the following variables: age, site, hypertension, diabetes, duration of HIV infection, nadir

TABLE 2. MULTIVARIATE LOGISTIC REGRESSION OF FACTORS ASSOCIATED WITH RENAL IMPAIRMENT AMONG HIV-INFECTED PATIENTS

Factor	OR	95% CI	p Value
Age per 10 year increase Hypertension	1.99 1.98	1.22-3.24 0.74-5.28	0.006
Nadir CD4 count per 100 cell	0.61	0.40-0.92	0.02
Duration of tenofovir per year	1.54	1.10-2.15	0.01

OR, odds ratio; CI, confidence interval.

CD4 cell count, current CD4 count, and duration of tenofovir use (or tenofovir with protease inhibitor). Table 2 shows the reduced (final) multivariate logistic regression model. Increasing age (OR 2.0 per 10 years, p = 0.006), lower CD4 nadir count (OR 0.6 per 100 cell change, p = 0.02), and duration of tenofovir use (OR 1.5 per year of use, p = 0.01) remained independently associated with renal dysfunction. Hypertension

was no longer significantly associated with renal dysfunction (OR 2.0, p = 0.17) and neither was the site. The second multivariate model had the similar findings, but tenofovir with a protease inhibitor was not significantly associated with renal dysfunction and dropped from the final model.

In order to further explore the risk factors for tenofovirassociated nephrotoxicity, a subset analysis was performed among the subjects currently receiving tenofovir (n = 318). Among subjects receiving tenofovir, 39% (n = 125) had an eGFR < 90, 4% (n = 13) had an eGFR < 60, and none had an eGFR of <30 mL/min/1.73 m². This subgroup was predominantly male (91%) with a median age of 42 years (IQR 37–48). Fifty-two percent (n = 165) were Caucasian, 33% (n = 106) were African American, 14% (n = 46) were other races; in one participant race was missing. Thirty-one percent (n = 99) were hypertensive and 10% (n = 31) had diabetes mellitus. The median duration of HIV infection was 14 years (IQR 8-17) and 43% (n = 138) had a nadir CD4 cell count <200 cells/mm³. The median current CD4 cell count was 482 cells/mm³ (IQR 342–663) and 56% (n = 176) had undetectable viral load. Sixty

TABLE 3. UNIVARIATE AND MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH RENAL DYSFUNCTION AMONG HIV-INFECTED PERSONS RECEIVING TENOFOVIR

	Normal renal function n = 305	Renal dysfunction ^b n = 13	Univariate			Multivariate		
Factor ^a			OR	95% CI	p Value	OR	95% CI	p Value
Age per 10 years	42 (37–47)	51 (41–62)	2.85	1.60-5.10	<0.001	2.89	1.53-5.45	0.001
Gender, male	278 (91.2)	12 (92.3)	0.86	0.11-6.85	0.89			
Ethnicity ^c								
Caucasian	158 (52.0)	7 (53.9)	1.0					
African American	102 (33.5)	4 (30.8)	0.89	0.25-3.10	0.85			
Other	44 (14.5)	2 (15.4)	1.01	0.45-2.26	0.98			
Site	. ,							
San Diego	172 (56.4)	9 (69.2)	1.0					
Bethesda	133 (43.6)	4 (30.8)	0.57	0.17-1.91	0.37			
Diabetes	27 (8.9)	4 (30.8)	4.56	1.32-15.8	0.02			
Hypertension	91 (29.8)	8 (61.5)	3.76	1.20-11.81	0.02			
Chronic hepatitis B	20 (6.6)	0 (0)	_		_			
Chronic hepatitis C	13 (4.3)	1 (7.7)	1.87	0.23-15.5	0.56			
Trimethoprim-sulfamethaxazole use	34 (11.2)	3 (23.1)	2.39	0.63-9.12	0.20			
Triglycerides per 30 mg/dL increase	154 (106-245)	138 (90–363)	1.02	0.93-1.12	0.70			
Total cholesterol per 30 mg/dL increase	183 (155-210)	210 (161-235)	1.02	0.93-1.11	0.72			
LDL per 30 mg/dL increase	106 (82–126)	118 (103-150)			0.08			
HDL per 10 mg/dL increase	37 (32-45)	39 (35-45)		0.66-1.64	0.86			
Duration of HIV infection, years	13.5 (8-17)	16.5 (14–18)	1.14	1.00-1.32	0.046			
CD4 nadir per 100 cells		· · ·						
Median (İQR)	226 (129-303)	80 (8-107)	0.36	0.19-0.68	0.002	0.35	0.71-0.73	0.005
<200	127 (41.6)	11 (84.6)	7.71	1.68-35.38	0.009			
≥200	178 (55.4)	2 (15.4)	1.00					
Current CD4 per 100 cells	· · ·	. ,						
Median (IQR)	490 (343-664)	392 (266-487)	0.82	0.63-1.07	0.14			
<350	78 (25.6)	5 (38.5)	1.00					
350500	80 (26.2)	5 (38.5)	0.98	0.27-3.50	0.97			
>500	147 (48.2)	3 (23.0)	0.56	0.27-1.17	0.12			
Log10 HIV RNA	1.7 (1.7–2.4)	1.7 (1.7–3.3)	1.18	0.66-2.13	0.57			
HIV RNA <50 copies/mL	169 (55.6)	7 (53.9)	0.93	0.31-2.84	0.90			
Concurrent protease inhibitor	182 (59.7)	10 (76.9)	2.25	0.61-8.35	0.22			
Didanosine use	42 (13.8)	3 (23.1)	1.88	0.50-7.11	0.35			

Factor expressed as number (percentage) for categorical variables and as median (interquartile range) for continuous variables.

^bRenal impairment defined as an estimated glomerular filtration rate of $<60 \text{ mL/min}/1.73\text{m}^2$ by the MDRD equation. Ethnicity was missing for one participant.

OR, odds ratio; CI, confidence interval; LDL, low-density lipoprotein; HDL, high density lipoprotein; IQR, interquartile range; MDRD, modification of Diet in Renal Disease.

percent (n = 192) were concurrently receiving protease inhibitor.

Among subjects receiving tenofovir, univariate analyses showed that older age, diabetes, hypertension, longer duration of HIV infection, and lower CD4 nadir were significantly associated with renal dysfunction (defined as an eGFR < 60 mL/min/1.73 m²; Table 3). There was a trend for higher low-density lipoprotein (LDL) and renal dysfunction, but this was not significant (OR 1.5 per 30 mg/dL increase, p = 0.08). In the multivariate model, the variables included were age, diabetes, hypertension, duration of HIV infection, nadir CD4 count, and LDL level. In the final model, older age and lower CD4 nadir were associated with renal dysfunction among HIV patients receiving tenofovir.

Two hundred forty-one (34%) participants initiated tenofovir and had data on the change in eGFR during the 2 years before and after tenofovir use. Characteristics of this group included a median age of 43 (IQR 39–49) years, 93% were male, and ethnicity was Caucasian in 53%, African American among 32%, and other among 15%. Ninety-three (31%) had hypertension and 33 (14%) diabetes. The median HIV duration was 14.5 (IQR 11–18) years, median CD4 nadir was 214 (99–288) cells/mm³, and 151 (63%) were concurrently receiving a protease inhibitor.

Of the HIV-infected persons initiating tenofovir, 120 (50%) had a reduction in their eGFR after tenofovir initiation. Of those who had a loss in renal function, the median decline in eGFR was $-10.5 \,\text{mL/min}/1.73 \,\text{m}^2$ (95% confidence interval [C] -8.9 to -13.3). A mean loss of $>10 \,\text{mL/min}/1.73 \,\text{m}^2$ was

experienced by 65 (27%) patients on tenofovir and a loss of $>30 \text{ mL/min}/1.73 \text{ m}^2$ by 14 (5.8%) patients during the 2-year follow-up period. Those initiating both tenofovir and a boosted PI had slightly greater changes in kidney function to the overall tenofovir group: 78 (52%) had a reduction in eGFR (median -12.1 ml/min/1.73m², 95% CI, -9.1 to -14.1), and 30% had a loss of >10 mL/min/1.73 m², but these differences were not statistically significant.

Although a similar proportion of those initiating HAART not containing tenofovir (n = 151) had a reduction in eGFR (55%, p = 0.35) than those on a tenofovir regimen, the median decline was smaller in the nontenofovir group ($-6.2 \text{ mL}/\text{min}/1.73 \text{ m}^2$, 95% CI, -5.4 to -7.3, p < 0.001). The percentage of non-tenofovir users with a renal loss of >10 and >30 mL/min/1.73 m² was significantly less than among tenofovir users (14% versus 27%, p = 0.003; 1% versus 6%, p = 0.03, respectively). Median changes in the eGFR after initiation of tenofovir and non-tenofovir HAART regimens among those who loss renal function are shown in Fig. 1.

In the univariate linear regression analyses, factors significantly associated with loss of renal function measured by the eGFR among those initiating tenofovir included female gender (β_{Coef} -42.7, 95% CI -49.6 to -35.9, p < 0.001), African American compared to Caucasian ethnicity (β_{Coef} -6.9, 95% CI -11.3 to -2.5, p = 0.002), low CD4 nadir (β_{Coef} 3.22 per 100 cells, 95% CI 1.45 to 4.98, p < 0.001), and undetectable HIV RNA (β_{Coef} -5.2, 95% CI -9.7 to -0.7, p = 0.02). There were no significant associations with age, diabetes, hypertension, lipid levels, duration of HIV

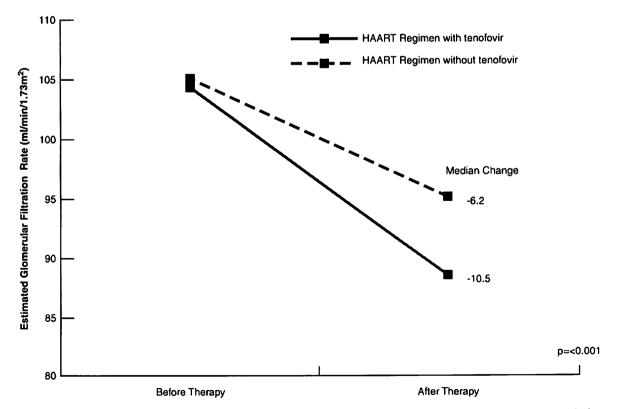


FIG. 1. Renal function before and after initiation of tenofovir and nontenofovir highly active antiretroviral therapy (HAART) regimens. Time points show mean estimated glomerular function rate for the 2 years before and after antiretroviral initiation.

infection, or current CD4 count, or current use of a protease inhibitor or didanosine.

In the multivariate model, predictors of a decline in renal function after tenofovir initiation included female gender (β_{Coef} -41.0, 95% CI -34.3 to -47.6, p < 0.001), African American ethnicity (β_{Coef} -5.2, 95% CI -1.7 to -8.6, p = 0.003), and lower CD4 nadir counts (β_{Coef} 2.16 per 100 cells, 95% CI 0.8–3.5, p = 0.002). In further exploration of the CD4 nadir using categorical data, those with a nadir <200 cells/mm³ was associated with renal loss after tenofovir initiation (β_{Coef} -6.7, 95% CI -11.1 to -2.28, p = 0.003), whereas the risk was not significantly different among those with a CD4 nadir of 200–350 cells/mm³ compared to >350 cells/mm³ (β_{Coef} 5.34, 95% CI - 5.39 to 6.46, p = 0.86). Similar findings were found when the outcome of a renal loss of >10 mL/min/1.73m² after tenofovir initiation was examined.

Discussion

The prevalence of renal impairment as defined by an eGFR < 60 mL/min/1.73 m² among HIV patients in our cohort was 3%. Our findings were consistent with the prevalence of 3.5% shown in a retrospective study of the predominantly Caucasian EuroSIDA cohort.¹² However, our study had a lower prevalence of eGFR values of 60–90 cc/mL compared with that of some studies.²²⁻²⁴ Discordance may be explained by variations in patient population characteristics including demographic characteristics, stage of HIV infection, and access to health care services. Of note, our population was relatively young (median age 41 years), was diagnosed with HIV relatively early in the course of infection, and had open access to medical care.

Factors associated with renal dysfunction in our HIV population included older age and lower CD4 nadir counts. Older age is an established risk factor for a decline in creatinine clearance in the general population.²⁵ Similarly, older age has been independently associated with renal function decline among HIV-infected subjects.^{12,24,26} Regarding low CD4 nadirs, our findings are concordant with other studies showing that prior AIDS and a history of low CD4 counts are risk factors for future kidney disease.¹² These data suggest that avoiding the occurrence of low CD4 cell counts, by early HIV diagnosis and treatment, may be important components of preventing future kidney disease among HIV patients; further studies are needed.

In addition to age and CD4 nadir counts, duration of tenofovir use was also significantly associated with renal dysfunction. Early clinical trials revealed a low incidence of renal dysfunction among HIV patients who received tenofovir.^{15,16} As more HIV patients were prescribed tenofovir, reports of Fanconi syndrome and renal proximal tubulopathy associated with tenofovir were published.^{27–29} Subsequent studies have demonstrated tenofovir use as a predictor of renal impairment.^{10,12–14,30,31} Similar to our study, a recent analysis linked the cumulative exposure of tenofovir to renal failure,¹² suggesting that long-term use of this medication may result in an increasing risk of nephrotoxicity.³²

We examined the risk factors for renal function decline among patients initiating tenofovir therapy. Our study had the advantage of evaluating eGFR measurements before and after tenofovir initiation. We found that female gender, African American ethnicity, and a CD4 nadir of <200 cells/ mm³ were risk factors for declining renal function after starting tenofovir. Our study findings are novel and may provide assistance in determining which patients may be at particular risk for tenofovir-associated nephrotoxicity. The findings that females and African Americans have a higher risk of renal loss after tenofovir could be related to differing metabolic rates and drug concentrations, although this requires further study. Previous reports have emphasized the disproportionate prevalence of kidney disease among African Americans⁹; our study suggests that this group also may be at particular risk for tenofovir-related nephrotoxicity. Our finding regarding female gender and renal dysfunction requires validation in HIV cohorts with more female participants given the small number of females evaluated in our study.

Patients who had low CD4 nadirs were also at risk of renal function decline after tenofovir initiation in our study. Prior studies also suggested that a history of an AIDS-defining diagnosis is a risk for tenofovir nephrotoxicity³³; these findings may be related to prior renal insults and existing subclinical renal disease. Prior studies have also suggested that concomitant diseases such as hypertension, diabetes, or chronic active hepatitis may be risk factors for tenofovir-related nephrotoxicity.^{33,34} Overall, these data suggest that these potential risk factors should be considered before starting antiretroviral regimens that include tenofovir. In addition, consideration of more frequent monitoring of kidney function may be useful after starting tenofovir in these patient groups³⁵; further studies are needed to determine specific guidelines.

Retrospective studies have suggested that protease inhibitors may also be risk factors for tenofovir-associated renal dysfunction.^{13,36} More recently, prospective observational studies have demonstrated that subjects who concurrently received tenofovir and a ritonavir-boosted protease inhibitor (most often lopinavir/ritonavir) had a statistically significant decline in renal function compared to those who received non-nucleoside reverse transcriptase inhibitors with tenofovir.^{18,31} In addition, a recent series of 164 cases of tenofovirassociated Fanconi syndrome showed that most patients were concurrently receiving a protease inhibitor, especially one that was boosted with ritonavir.²⁹ These studies suggest a synergistic effect of tenofovir plus a protease inhibitor in the development of renal dysfunction; in our study, the tenofovirprotease inhibitor association showed borderline significance. The mechanism of a tenofovir/boosted protease inhibitor combination leading to a decline in GFR is unclear, but may be explained by drug-drug interactions.37 We did not find an increased risk of renal dysfunction with concurrent use of didanosine use described in prior studies,^{29,36} perhaps due to the limited use of this medication among our study population.

Our study has a number of potential limitations given the cross-sectional study design; primary is the issue that temporality could not be established between each factor and the development of renal dysfunction. We did, however, examine changes in kidney function before and after use of tenofovir therapy, and factors associated with renal loss during this interval. We acknowledge that given the low prevalence of renal dysfunction in our cohort, we may have missed factors associated with renal disease. Our study did not collect data

RENAL DYSFUNCTION IN HIV PATIENTS

on the presence of proteinuria, an early sign of renal dysfunction among patients with normal GFR.⁹ Consequently, the prevalence of renal impairment among subjects with $eGFR > 60 \,mL/min/1.73 \,m^2$ may have been underestimated. In addition, for our analyses of kidney function over time among patients using tenofovir, we examined only those who remained on tenofovir, hence may have missed early medication-associated renal dysfunction in this group. Furthermore, since HIV patients with worse renal function may be less likely to initiate tenofovir, this could also have resulted in an underestimation of its effect. Impaired kidney function due to acute renal failure versus gradually developing chronic renal insufficiency was not differentiated in this study. In addition, calculations of eGFR were based on single measurements of serum creatinine, which may be subject to variations due to laboratory or patient factors. Last, there may be inherent differences between our military population and the general population which may limit our ability to generalize our findings to the U.S. population.

In summary, our study contributes to the current knowledge regarding HIV patients who may be at greatest risk for kidney dysfunction in the ambulatory setting. Our study suggests that longer duration of tenofovir use is associated with renal dysfunction and that among HIV patients initiating tenofovir therapy, those who are female, African American, or have CD4 nadirs of <200 cells/mm³ may be at highest risk for renal function loss. Further studies are needed to determine if differential guidelines on kidney function monitoring in select HIV populations would be beneficial.

Acknowledgments

The content of this publication is the sole responsibility of the authors and does not necessarily reflect the views or policies of the NIH or the Department of Health and Human Services, the Department of Defense (DoD) or the Departments of the Army, Navy or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government. The authors have no commercial or other association that might pose a conflict of interest in this work.

Support for this work was also provided by the Infectious Disease Clinical Research Program (IDCRP), a DoD program executed through the Uniformed Services University of the Health Sciences. This project has been funded in whole, or in part, with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), under Inter-Agency Agreement Y1-AI-5072.

This work is original and has not been published elsewhere. An abstract containing some of these data was presented in part at the Infectious Diseases Society of America Meeting in 2006 and the International AIDS Conferences in 2006 and 2007.

Author Disclosure Statement

No competing financial interests exist.

References

 Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-Infected patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2005;40:1559-1585.

- Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;388:853–860.
- Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: Changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43:27–34.
- Schwartz EJ, Szczech LA, Ross MJ, Klotman ME, Winston JA, Klotman PEI. Highly active antiretroviral therapy and the epidemic of HIV+ end-stage renal disease. J Am Soc Nephrol 2005;16:2412-2420.
- Winston JA, Klotman ME, Klotman PE: HIV-associated nephropathy is a late, not early, manifestation of HIV-1 infection. Kidney Int 1999;55:1036–1040.
- Szczech LA, Gupta AK, Ramez H, et al. The clinical epidemiology and course of the spectrum of renal diseases with HIV infection. Kidney Int 2004;66:1145–1152.
- Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: A 12-year cohort study. AIDS 2004;18:541–546.
- Choi AI, Shlipak MG, Hunt PW, Martin JN, Deeks SG. HIVinfected persons continue to lose kidney function despite successful antiretroviral therapy. AIDS 2009;23:2143–2149.
- Fine DM, Atta MG. Kidney disease in the HIV-infected patient. AIDS Patient Care STDs 2007;21:813–824.
- Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis 2005;40:1194–1198.
- Winston A, Amin J, Mallon P, et al. Minor changes in calculated creatinine clearance and anion-gap are associated with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy. HTV Med 2006;7:105–111.
- Mocroft A, Kirk O, Gatell J, et al. Chronic renal failure among HIV-infected patients. AIDS 2007;21:1119–1127.
- Fux CA, Simcock M, Wolbers M, et al. Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. Antiviral Ther 2007;12: 1165–1173.
- Horberg M, Tang B, Towner W, et al. Impact of tenofovir on renal function in HIV-infected antiretroviral naïve patients. J Acquir Immune Defic Syndr 2010;53:62–69.
- Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: Results from a 48-week, randomized, double-blinded study. AIDS 2002;16:1257–1263.
- Jones R, Stebbing J, Nelon M, et al. Renal dysfunction with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy regimens is not observed more frequently: A cohort and case-control study. J Acquir Immune Defic Syndr 2004;37:1489–1495.
- Gallant JE, Winston JA, DeJesus E, et al. The 3-year renal safety of a tenofovir disoproxil fumarate vs. a thymidine analogue-containing regimen in antiretroviral-naive patients. AIDS 2008;22:2155–2163.
- Gallant JE, Moore RD. Renal function with use of a tenofovir-containing initial antiretroviral regimen. AIDS 2009; 23:1971–1975.
- Izzedine H, Hulot JS, Vittecoq D, et al. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviralnaive HIV-1-infected patients. Data from a double-blind

randomized active-controlled multicentre study. Nephrol Dial Transplant 2005;20:743-746.

- Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;45:247–254.
- Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. National Kidney Foundation. www.kidney.org/professionals/KDOQI/guidelines_ckd/p4_ class_g1.htm (Last accessed June 1, 2009).
- Fernando SK, Finkelstein FO, Moore BA, Weissman S. Prevalence of chronic kidney disease in an urban HIV infected population. Am J Med Sci 2008;335:89–94.
- Lucas GM, Mehta SH, Atta MG, et al. End-stage renal disease and chronic kidney disease in a cohort of African American HIV-Infected and at-risk HIV-seronegative participants followed between 1988 and 2004. AIDS 2007;21: 2435-2443.
- Wyatt CM, Winston JA, Malvestutto CD, et al. Chronic kidney disease in HIV infection: An urban epidemic. AIDS 2007;21:2101-2110.
- Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J Clin Invest 1950;29:496–507.
- Cheung CY, Wong KM, Lee MP, et al. Prevalence of chronic kidney disease in Chinese HIV-infected patients. Nephrol Dialysis Transplant 2007;22:3186–3190.
- Schaaf B, Aries SP, Kramme E, Dalhoff K. Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. Clin Infect Dis 2003; 37:e41-e43.
- Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: Three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis 2003; 36:1070–1073.
- 29. Gupta SK. Tenofovir-associated Fanconi syndrome: Review of the FDA adverse event reporting system. AIDS Patient Care STDs 2008;22:99–103.

- Overton ET, Nurutdinova D, Freeman J, Seyfried W, Mondy KE. Factors associated with renal dysfunction within an urban HIV-infected cohort in the era of highly active antiretroviral therapy. HIV Med 2009;10:343–350.
- Goicoechea M, Liu S, Best B, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. J Infect Dis 2008;197:102–108.
- 32. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. AIDS Res Hum Retroviruses 2009;25:387–394.
- Madeddu G, Quirino T, Carradori S, et al. Renal toxicity in HIV-infected patients receiving HAART including tenofovir. Infez Med 2006;14:125–134.
- 34. Tan LK, Gilleece Y, Mandalia S, et al. Reduced glomerular filtration rate but sustained virologic response in HIV/ hepatitis B co-infected individuals on long-term tenofovir. J Viral Hepat 2009;16:471–478.
- 35. Young B, Buchacz K, Moorman A, Wood KC, Brooks JT; HIV Outpatient Study (HOPS) Investigators. Renal function in patients with preexisting renal disease receiving tenofovir-containing highly active antiretroviral therapy in the HIV outpatient study. AIDS Patient Care STDs 2009;23: 589-592.
- Crane HM, Kestenbaum B, Harrington RD, et al. Amprenavir and didanosine are associated with declining kidney function among patients receiving tenofovir. AIDS 2007; 21:1431–1439.
- Zimmerman AE, Pizzoferrato T, Bedford J, et al. Tenofovirassociated acute and chronic kidney disease: A case of multiple drug interactions. Clin Infect Dis 2006;42:283–290.

Address correspondence to: Nancy Crum-Cianflone, M.D., M.P.H. c/o Clinical Investigation Department (KCA) Naval Medical Center San Diego 34800 Bob Wilson Drive, Suite 5 San Diego, CA 92134-1005

E-mail: nancy.crum@med.navy.mil

This article has been cited by:

- Shikha Garg, Melanie Hoenig, Erika M. Edwards, Caleb Bliss, Timothy Heeren, Sheila Tumilty, Alexander Y. Walley, Margaret J. Koziel, Paul R. Skolnik, C. Robert Horsburgh, Deborah Cotton. 2011. Incidence and Predictors of Acute Kidney Injury in an Urban Cohort of Subjects with HIV and Hepatitis C Virus Coinfection. *AIDS Patient Care and STDs* 25:3, 135-141. [Abstract] [Full Text] [PDF] [PDF Plus]
- 2. Robert Kalyesubula, Mark A. Perazella. 2011. Nephrotoxicity of HAART. AIDS Research and Treatment 2011, 1-11. [CrossRef]