Risk factors for chronic kidney disease in a large cohort of HIV-1 infected individuals initiating antiretroviral therapy in routine care

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Objective: To examine long-term effects of antiretroviral therapy (ART) on kidney function, we evaluated the incidence and risk factors for chronic kidney disease (CKD) among ART-naive, HIV-infected adults and compared changes in estimated glomerular filtration rates (eGFR) before and after starting ART.

Methods: Multicenter observational cohort study of patients with at least one serum creatinine measurement before and after initiating ART. Cox proportional hazard models, and marginal structure models examined CKD risk factors; mixed-effects linear models examined eGFR slopes.

Results: Three thousand, three hundred and twenty-nine patients met entry criteria, contributing 10 099 person-years of observation on ART. ART was associated with a significantly slower rate of eGFR decline (from −2.18 to −1.37 ml/min per 1.73 m^2 per year; $P = 0.02$). The incidence of CKD defined by eGFR thresholds of 60, 45 and 30 ml/min per 1.73 m^2 was 10.5, 3.4 and 1.6 per 1000 person-years, respectively. In adjusted analyses black race, hepatitis C coinfection, lower time-varying CD4 cell count and higher time-varying viral load on ART were associated with higher CKD risk, and the magnitude of these risks increased with more severe CKD. Tenofovir and a ritonavir-boosted protease inhibitor (rPI) was also associated with higher CKD risk [hazard odds ratio for an eGFR threshold <60 ml/min per 1.73 m^2: 3.35 (95% confidence interval (CI) = 1.40–8.02)], which developed in 5.7% of patients after 4 years of exposure to this regimen-type.

Conclusion: ART was associated with reduced CKD risk in association with CD4 cell restoration and plasma viral load suppression, despite an increased CKD risk that was associated with initial regimens that included tenofovir and rPI.

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Introduction

Treatment with potent combination antiretroviral therapy (ART) is associated with lower incidence of HIV-associated nephropathy (HIVAN) [1] and improved kidney function [2–5], but information about the long-term benefits of ART on kidney function is lacking. HIV-infected individuals have a greater risk of chronic kidney disease (CKD) than the general age-matched population and kidney function may continue to decline despite

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ART [6,7]. As in the general population, HIV-infected patients with CKD have higher risk of cardiovascular disease and all-cause mortality [8,9].

Although ART may improve kidney function, nephrotoxicity has been observed with some drugs. Many studies have identified nephrotoxicity in association with tenofovir [10–18]. Nephrotoxicity also was associated with atazanavir [17,19], whereas some but not all studies have described enhanced nephrotoxicity when tenofovir was combined with atazanavir or a ritonavir-boosted protease inhibitor (rPI), suggesting additive toxicity or interactions between drugs [20–24]. However, most previous studies examined the effects of individual drugs rather than drug regimens on kidney function.

To better understand the long-term benefits and risks of ART on kidney function among the broader spectrum of HIV-1 infected patients in routine care, we sought to determine the incidence of moderate and severe CKD in association with demographic factors, comorbid conditions, CD4 cell count, and plasma HIV-1 viral load during treatment, and we compared changes in estimated glomerular function (eGFR) before and after ART-initiation in a large multicenter cohort of ART-naive patients from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort [25]. To further explore nephrotoxicity associated with tenofovir, and to specifically examine whether a rPI may enhance this toxicity, we also compared CKD risk by initial ART regimens that were categorized into four mutually exclusive regimen-types according to whether they included a rPI or a nonnucleoside reverse transcriptase (NNRTI), with or without tenofovir.

Methods

CNICS comprises a large, diverse population of HIV-1 infected patients receiving care at eight clinical sites that are affiliated with the Centers for AIDS Research, an interdisciplinary collaboration of basic and clinical investigators distributed across the United States [25]. Comprehensive clinical data captured in point-of-care electronic health records, including medications, laboratory results, and diagnoses undergo rigorous quality assessment and standardization, and are integrated into a single data repository. Patients without prior ART of any kind, with at least one serum creatinine before and after initiating ART between April 1996 and July 2009 were included. ART was defined as three or more drugs, including a nonnucleoside reverse transcriptase inhibitor or a rPI. To enhance the generalizability of our findings with current ART treatment guidelines, patients were excluded whose initial regimen included indinavir, two or more protease inhibitors (not including ritonavir), a protease inhibitor and a NNRTI, or an unboosted protease inhibitor. Because of small numbers of initial regimens that included raltegravir and maravaroc these regimens were also excluded. Initial regimens were categorized into four mutually exclusive regimen-types as tenofovir and a rPI; tenofovir and a NNRTI; a rPI without tenofovir; and a NNRTI without tenofovir, to which the other three regimens were compared.

Laboratory measurements were collected at the discretion of the clinician during routine care according to guidelines for HIV-disease management [26]. We estimated eGFR by the four variable Modification of Diet and Renal Disease (MDRD) equation. In sensitivity analyses, eGFR was also measured using the CKD-Epidemiology equation [27]. In accordance with recently proposed revisions to the classification of CKD, moderate CKD (stage 3) was subdivided by eGFR thresholds of less than 60, and less than 45 ml/min per 1.73 m^2; severe CKD (stage 4) was defined by a threshold of less than 30 ml/min per 1.73 m^2 [28,29]. Qualifying values included those measurements that fell below each threshold and persisted for at least 3 months, during which time the median value of all eGFR measurements also had to remain below these thresholds. Cases of moderate CKD also included those with more advanced stages. CNICS is approved by the Institutional Review Boards at each CNICS site.

We used standard Cox proportional hazards models to examine risk factors for CKD at each eGFR threshold. Patients were included who had an eGFR more than 60 ml/min per 1.73 m^2 at the last pre-ART measurement, and did not have a prior diagnosis of kidney disease, determined by their physician. We examined the following baseline patient factors before ART initiation: AIDS-defining illness (ADI), pharmacologically treated hypertension and diabetes, chronic hepatitis B (hepatitis B surface antigen positive) and C (detectable hepatitis C RNA), nadir CD4 cell count, latest pre-ART HIV-1 viral load; and also examined time-varying CD4 cell count and viral load after ART initiation using the last value-carried-forward method for missing time-varying measurements. Time at risk began upon ART initiation and continued until the onset of CKD (determined by the first qualifying eGFR value) and patients were censored upon death, lost-to-follow-up, or at the conclusion of the study, whichever occurred first. Each risk factor was examined in a separate model adjusted for age, sex, race, last pre-ART eGFR and initial ART regimen-type. All patients were included in these analyses whether or not they remained on their initial ART regimen.

We used marginal structural pooled logistic regression models to examine associations between initial ART regimen exposure and CKD risk by censoring patients upon any change in ART, in addition to censoring for the reasons specified above, and adjusting for potential bias introduced by this informative censoring. Because initial

ART regimens were not assigned at random, we also controlled for potential confounding by indication in these models using inverse probability treatment weights for differences between initial ART regimen-types among the following baseline covariates: age, sex, race (black versus not black), prior (ADI), pharmacologically treated hypertension and diabetes, chronic hepatitis B and C infections, nadir CD4 cell count and the last pre-ART eGFR and viral load, using a random forest approach [30]. Inverse probability weights for regimen change were estimated within uniform 12-week intervals to adjust for possible informative censoring using all of the above baseline variables and the initial ART regimen-type, and the following time-varying covariates after ART initiation: CD4 cell count and viral load [31,32]. Finally, we explored interactions between all baseline factors and the initial ART regimen-type and we used a cumulative incidence analysis to estimate the proportion of patients with CKD according to the initial ART regimen-type, in which death was treated as a competing risk [33].

Linear eGFR slopes before and after ART initiation were estimated by mixed-effects linear spline models that included all available serum creatinine measurements before and after ART initiation, with a knot at the time of ART initiation. These models were adjusted for initial ART regimen-type, chronic hepatitis B and C infections, pharmacologically treated hypertension and diabetes, time-varying CD4 cell count and viral load, and incorporated all eGFR measurements, whether or not patients remained on their original ART. They used random intercepts and slopes, and assumed an unstructured covariance matrix. Statistical significance was defined as $P < 0.05$ in all analyses, which used R (version 2.10.1), or SAS (version 9.0; SAS Institute Inc., Cary, North Carolina, USA).

Results

Three thousand, three hundred and twenty-nine patients met study entry criteria and initiated 15 distinct ART regimens (categorized into four ART regimen-types as above) between April 1996 and July 2009 (Table 1) The median follow-up duration was 4.8 years [231 weeks; interquartile range (IQR) 121–364 weeks] including a median of 23 weeks (IQR 6–115 weeks) before, and 143 weeks after ART-initiation (IQR 61–255 weeks). Patients had a median of three (IQR 1–8) and 13 (IQR 6–25) creatinine measurements before and after initiating ART, respectively, with a cumulative follow-up duration of 10 990 person-years on ART. The majority of patients (2176; 64%) remained on their original ART regimen throughout follow-up, including 83 and 73% of patients, who received tenofovir and an NNRTI or a rPI, respectively, and 46 and 38% of patients, who received a NNRTI or a rPI, respectively, without tenofovir ($P < 0.001$ for comparisons between tenofovir plus a NNRTI versus the other three regimen types). Among patients, who had a change in their initial ART, this occurred after a median of 79 weeks (IQR 33–166 weeks). One hundred and sixty-seven patients died during follow-up a median of 122 weeks (IQR 53–212 weeks) after starting ART. Additional characteristics of the study cohort are summarized in Table 1.

Table 1. Distribution of baseline demographic and clinical characteristics among all patients, and according to the initial antiretroviral therapy regimen types as: tenofovir (TDF) with a ritonavir-boosted protease inhibitor (rPI), TDF with a nonnucleoside reverse transcriptase inhibitor (NNRTI), a rPI without TDF, and a NNRTI without TDF.

Baseline characteristics	All	TDF^+/rPI	TDF^+/NNRTI	TDF^-/rPI	TDF^-/NNRTI
N (%)	3329	828 (24.9)	1169 (35.1)	396 (11.9)	936 (28.1)
Age (years) at ART initiation median (IQR)	40 (37, 42)	40 (39, 42)	41 (40, 43)	38 (37, 40)	36 (35, 38)
Female *n* (%)	622 (18.7)	160 (19.3)	153 (13.1)	108 (27.3)	201 (21.5)
Black *n* (%)	1281 (38.5)	248 (30.0)	386 (33.0)	188 (47.5)	459 (49.0)
Prior AIDS-defining illness (ADI) *n* (%)	964 (29.0)	264 (31.9)	223 (19.1)	166 (41.9)	311 (33.2)
Hypertensionn (%)	535 (16.1)	125 (15.1)	170 (14.5)	76 (19.2)	164 (17.5)
Diabetes *n* (%)	107 (3.2)	20 (2.4)	36 (3.1)	20 (5.1)	31 (3.3)
HCV *n* (%)	496 (14.9)	140 (16.9)	135 (11.5)	62 (15.7)	159 (17.0)
HBV *n* (%)	181 (5.4)	52 (6.3)	86 (7.4)	10 (2.5)	33 (3.5)
Pre-ART $\log_{10}$ HIV-1 viral loadcopies/ml median (IQR)	4.9 (4.4, 5.3)	5.0 (4.6, 5.4)	4.8 (4.3, 5.2)	5.1 (4.5, 5.5)	4.9 (4.5, 5.4)
Pre-ART nadir CD4 cells/μl median (IQR)	207 (72, 316)	188 (62, 300)	251 (132, 346)	120 (27, 266)	190 (59, 310)
Pre-ART eGFR ml/min per 1.73 m^2 median (IQR)	100 (86, 118)	100 (87, 118)	99 (87, 114)	101 (80, 118)	104 (89, 122)
rPI or NNRTI component of initial ART regimen, *n* (%)					
rAmprenavir		536 (65)	–	15 (4)	–
rAtazanivir		–	–	77 (19)	–
rLopinavir		292 (35)	–	271 (69)	–
rSaquinavir		–	–	33 (2)	–
Efavirenz		–	1142 (98)	–	896(96)
Nevaripine		–	27 (2)	–	40 (4)

ART, antiretroviral therapy; CI, confidence interval; CKD, chronic kidney disease; HCV, hepatitis C virus; HBV, hepatitis B virus; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; rPI, ritonavir-boosted protease inhibitor; r, ritonavir; TDF, tenofovir. Hypertension and diabetes refers to pharmacologically treated patients with these diagnoses.

Factors associated with stage 3 or greater chronic kidney disease

New onset stage 3 or greater CKD, defined by an eGFR less than 60 ml/min per 1.73 m^2, developed in 106 patients a median of 45 weeks after ART initiation (IQR 11–137 weeks), with an incidence of 10.1 cases per 1000 person-years [95% confidence interval (CI) = 8.3–12.3]. Factors associated with significantly higher risk for CKD defined by this eGFR threshold included: black race, hepatitis C coinfection, pharmacologically treated hypertension, a prior ADI, lower CD4 nadir and lower time-varying CD4 cell count, higher last pre-ART viral load and higher time-varying viral load on ART in adjusted models (Table 2). The initial ART regimen-type was not significantly associated with increased CKD risk in these models.

Seventy-two patients developed stage 3 or greater CKD while on their original ART regimen. In marginal structural models controlling for informative censoring upon regimen change and confounding by indication, patients who received tenofovir and a rPI had a significantly higher risk of CKD than those treated with a NNRTI without tenofovir [hazard odds ratio (HOR) 3.35 (95% CI, 1.40–8.02), $P = 0.006$] (Table 3). Tenofovir and a NNRTI was not significantly associated with increased risk of CKD in these models [HOR 1.59 (95% CI, 43–5.87), $P = 0.48$]. Tenofovir and a rPI was associated with a similar trend towards higher CKD risk when eGFR was estimated by the CKD-Epidemiology equation [HOR: 2.44 (95% CI, 0.99–6.01), $P = 0.052$]. The cumulative incidence of CKD in patients, who received tenofovir and a rPI was 5.7% after 4 years.

Although patients were censored upon any change of initial ART in this analysis, similar associations with initial ART regimen-types were evident when we included cases that began within 6 months after changing ART [HOR for rPI and tenofovir 2.75 (95% CI, 1.20–6.28)]. Among rPI regimens, the risk of CKD with atazanavir was similar to that associated with protease inhibitors not including atazanavir [HOR: 2.23 (95% CI, 0.82, 6.06), $P = 0.12$ and 5.40 |(95% CI, 1.94–15.05), $P = 0.001$ with atazanavir–ritonavir, and rPI not including atazanavir, respectively]. Among baseline factors, only race modified the association between CKD and initial ART [HOR for CKD in patients, who received tenofovir and a rPI versus a NNRTI without tenofovir: 9.12 (95% CI, 2.06–40.32), and 1.08 (95% CI, 0.04–29.77) among nonblack, and black patients, respectively, *P*-value for interaction = 0.02].

Thirty-four patients developed stage 3 or greater CKD, defined by an eGFR threshold of 45 ml/min per 1.73 m^2 [incidence 3.3 cases per 1000 person-years (95% CI, 2.3–4.6)]. Black race, hepatitis C virus (HCV) coinfection, pharmacologically treated hypertension, a prior ADI, lower nadir and time-varying CD4 cell counts, and higher time-varying viral load remained significantly associated with this event, and the magnitude of risk for stage 3 or greater CKD was higher than when defined by a 60 ml/min per 1.73 m^2 threshold (Table 2). Initial ART regimens were not associated with increased risk of CKD defined by this threshold among all patients (Table 2), among the 20 patients who remained on their original regimen at the onset of this event (Table 3), or when including cases whose initial onset was within 6 months after changing ART (data not shown). However, 90% of stage 3 CKD events were lost in the marginal structural logistic regression analysis when the CKD threshold was changed from 60 to 45 ml/min per 1.73 m^2 among patients whose initial ART regimen contained tenofovir and a rPI, compared with only 50% of events lost among patients whose initial ART regimen contained tenofovir and a NNRTI, limiting the ability to estimate this effect.

Factors associated with stage 4 or greater chronic kidney disease

Sixteen patients developed stage 4 or greater CKD after ART initiation [incidence 1.6 cases per 1000 person-years (95% CI = 0.8–2.4 per 1000 person-years)]. Consistent with the previous analyses, the risk of stage 4 CKD remained significantly higher among blacks, in patients with HCV coinfection, with lower time-varying CD4 cell count and higher time-varying viral load, and again, the magnitude of risk increased compared to CKD defined by higher eGFR thresholds (Table 2).

Among all patients, whether or not they remained on their regimen at the onset of the event, the risk of stage 4 or greater CKD was not significantly associated with either of the two types of tenofovir-containing regimens in the Cox proportional hazards model (Table 2). There were too few patients (9) who developed stage 4 or greater CKD while on their original regimen to reliably estimate the risk of CKD by initial ART regimen-type.

One hundred and two patients began ART with preexisting kidney disease (defined by the last pre-ART eGFR <60, but ≥30 ml/min per 1.73 m^2), of whom 18 developed stage 4 CKD [eGFR <30 ml/min per 1.73 m^2; incidence 51.1 per 1000 person-years (95% CI = 30.2–80.8 per 1000 person-years)]. Initial ART regimen-types were not significantly associated with an increased risk of stage 4 or greater CKD, both among the 15 patients, who remained on their original regimen at the onset of this event or among all patients (data not shown).

Estimated glomerular function slopes before and after antiretroviral therapy initiation

eGFR slopes before and after ART initiation were approximately linear in models that used all creatinine measurements, whether or not patients remained on their original ART regimen. ART was associated with a

Table 2. Risk of chronic kidney disease by baseline factors and post antiretroviral therapy (ART) time-varying CD4 cell count and viral load from Cox proportional hazards models that include age, sex, race, pre-ART estimated glomerular filtration rate (eGFR) and initial ART regimen-type among all patients, whether or not they remained on their initial ART regimen at the onset of the event.

	CKD stage ≥3				CKD stage ≥4	
	<60 ml/min/1.73m^2		<45 ml/min per 1.73 m^2		<30 ml/min per 1.73 m^2	
	$N=106$		$N=34$		$N=16$	
Risk factors	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
TDF$^+$/rPI regimen vs. NNRTI without TDF	1.34 (0.75–2.40)	0.32	0.57 (0.18–1.82)	0.34	2.24 (0.22–23.15)	0.49
TDF$^+$/NNRTI regimen vs. NNRTI without TDF	0.49 (0.22–1.08)	0.08	0.43 (0.12–1.58)	0.20	1.89 (0.21–16.89)	0.57
Last Pre-ART eGFR for each 10 more ml/min per 1.73 m^2	0.43 (0.01–0.13)	<0.0001	0.80 (0.68–0.94)	0.005	0.79 (0.63–1.01)	0.06
Blackrace vs. not black	1.70 (1.06–2.74)	0.03	5.25 (2.16–12.79)	0.0003	17.03 (2.10–138.31)	0.008
[a]Pre-ART Nadir CD4 per every 100 more cells/μl	0.82 (0.68–0.98)	0.03	0.73 (0.53–1.00)	0.05	0.83 (0.54–1.29)	0.41
[a]Post-ART CD4 (time-varying) per every 100 more cells/μl	0.76 (0.67–0.86)	<0.0001	0.62 (0.49–0.79)	<0.0001	0.56 (0.37–0.85)	0.007
[a]Last pre-ART viral load per each increase by1 $\log_{10}$copies/ml	1.96 (1.28–3.00)	0.002	1.81 (0.93–3.50)	0.08	1.55 (0.61–3.95)	0.36
[a]Post-ART viral load (time-varying) per each increase by 1$\log_{10}$ copies/ml	1.31 (1.10–1.55)	0.003	1.48 (1.15–1.90)	0.002	2.01 (1.33–3.27)	0.001
[a]Pre-ART AIDS defining illness (ADI)	2.57 (1.64–4.01)	<.0001	3.13 (1.50–6.54)	0.003	2.38 (0.69–8.24)	0.16
[a]HCV coinfection	1.94 (1.18–3.20)	0.01	3.12 (1.51–6.45)	0.002	4.95 (1.56–15.68)	0.007
[a]Diabetes pharmacologically treated	2.17 (0.87–5.39)	0.09	0.83 (0.11–5.91)	0.83	2.12 (0.28–16.45)	0.47
[a]Hypertension pharmacologically treated	2.02 (1.25–3.26)	0.004	2.19 (1.02–4.71)	0.01	2.37 (0.30–18.50)	0.41

ART, antiretroviral therapy; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; rPI, ritonavir-boosted protease inhibitor; TDF, tenofovir. *N* is the number of events.

[a]Models for pre-ART nadir CD4, last pre-ART viral load, ADI, HCV, diabetes, hypertension, and post-ART time-varying CD4 and viral load were fit separately and adjusted for age, sex, race, pre-ART eGFR and ART regimen-type.

Table 3. Risk of stage ≥3 chronic kidney disease by the initial antiretroviral therapy regimen-type, estimated by hazard odds ratios using marginal structural logistic regression models that control for confounding by indication and time-varying informative censoring.

	eGFR <60 ml/min per 1.73 m^2		eGFR <45 ml/min per 1.73 m^2	
Initial ART regimen-type	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
TDF^+/rPI	3.35 (1.40–8.02)	0.006	0.24 (0.05–1.20)	0.08
TDF^+/NNRTI	1.59 (0.43–5.90)	0.48	1.39 (0.19–10.07)	0.73
TDF^-/rPI	1.04 (0.24–4.45)	0.95	0.33 (0.07–1.62)	0.17
TDF^-/NNRTI	Reference		Reference	

ART, antiretroviral therapy; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NNRTI, nonnucleoside reverse transcriptase inhibitor; rPI, ritonavir-boosted protease inhibitor; TDF, tenofovir.

significantly slower rate of eGFR decline [by 0.81 (95% CI, 0.03–1.59) ml/min per 1.73 m^2per year, $P = 0.02$] after adjusting for ART regimen-type, hepatitis B and C, pharmacologically treated hypertension and diabetes, and time-varying CD4 cell count and viral load (Table 4). When analyzed according to the initial ART regimen-type, eGFR improved compared with the corresponding pre-ART slope in association with each regimen-type, but this improvement was significant only for patients, who received tenofovir and a rPI (Table 4).

Discussion

In this large multicenter cohort of HIV-infected patients in routine care with a median follow-up duration of 4.8 years on ART, we observed a significantly slower rate of eGFR decline associated with antiretroviral treatment. We also observed a significantly higher risk of developing CKD in association with lower time-varying CD4 cell count and higher plasma viral load. This suggests that effective ART lowered the rate of eGFR decline and lowered the risk of CKD, and the magnitude of this protective effect increased in a dose-dependent manner with increasing severity of kidney disease. We also observed a significantly higher risk of moderate CKD associated with tenofovir and a rPI (HOR 3.35 for eGFR less than 60 ml/min per 1.73 m^2, compared with a regimen that included a NNRTI without tenofovir). Despite this high risk, however, moderate CKD was uncommon in association with this regimen-type, developing in 5.7% of patients after 4 years of exposure. Furthermore, regimens containing tenofovir and a rPI were not associated with a significantly increased risk of more severe kidney disease in the context of usual care that included regular toxicity monitoring, although the small number of cases may have limited our ability to detect such an association. Of note, we did not observe a significantly increased risk of CKD at any eGFR threshold in patients, who initiated tenofovir plus a NNRTI.

Previous studies have demonstrated kidney function improvements in patients with HIVAN [1,34–36], and in observational cohorts of HIV-infected with renal insufficiency [2,4–6,37]. In some studies, this improvement was associated with viral load suppression on ART [2,3]. Consistent with two large multicenter cohort studies showing higher risk of ESRD associated with lower last CD4 cell count on ART [38,39], we extend these findings by demonstrating a significantly higher risk of CKD with lower time-varying CD4 cell count and higher time-varying plasma viral load on ART. These results provide additional evidence for the benefits of ART on kidney function in HIV-infected patients.

Many studies have found modest nephrotoxicity associated with tenofovir [10–17,21]. In a meta-analysis of 17 studies, the magnitude of this effect was −3.9 ml/min

Table 4. Linear mixed model results for the change in estimated glomerular filtration rate over time according to initial antiretroviral therapy (ART) regimen type, controlling for ART regimen-type, chronic hepatitis B and C, pharmacologically treated hypertension and diabetes, and time-varying CD4 cell count and viral load.

	N	%	Pre-ART slope ml/min per 1.73 m^2 per year (95% CI)	Slope on ART ml/min per 1.73 m^2per year (95% CI)	Slope change ml/min per 1.73 m^2 per year (95% CI)
All patients	3329	100	−2.18 (−2.81 to −1.55)	−1.37 (−2.02 to −0.72)	0.81 (0.03 to 1.59)*
TDF^+/rPI	828	24.9	−2.10 (−2.98 to −1.22)	0.22 (−0.70 to 1.13)	2.32 (1.07 to 3.56)**
TDF^+/NNRTI	1169	35.1	−1.35 (−1.94 to −0.75)	−0.86 (−1.51 to −0.21)	0.49 (−0.81 to 1.80)
TDF^-/rPI	396	11.9	−3.91 (−7.77 to −0.05)	−1.11 (−5.02 to 2.80)	2.80 (−1.26 to 6.85)
TDF^-/NNRTI	936	28.1	−3.19 (−4.49 to −1.90)	−2.10 (−3.34 to −0.86)	1.09 (−0.23 to 2.42)

ART, antiretroviral therapy; CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; rPI, ritonavir-boosted protease inhibitor; TDF, tenofovir. nRapid eGFR declines are more than 4 ml/min per year [28]. Slope estimates for each ART regimen were analyzed separately.
*$P = 0.02$.
**$P = 0.0004$

over a median of 48 weeks [16]. Atazanavir was also independently associated with nephrotoxicity in one large study, and with enhanced nephrotoxicity when combined with tenofovir. Ritonavir may enhance tenofovir-associated nephrotoxicity by increasing tenofovir plasma levels, possibly via enhanced intestinal absorption [40,41]. In two clinical trials and two observational cohorts, greater eGFR declines were observed over 48 weeks to 24 months with tenofovir and a rPI, versus a NNRTI [20–23]. In contrast to our study, however, six observational studies did not find evidence of increased nephrotoxicity with tenofovir when it was combined with a rPI, including two that examined CKD risk and four that examined eGFR changes [10,14,17,18,24,42]. In the present study, the CKD risk associated with atazanivir–ritonavir did not appear to be different from that of other rPIs, mainly lopinavir–ritonavir. Although the reasons for discrepancies between the present study and several others are not apparent, it is possible that by examining outcomes associated with initial ART regimens only, we avoided obscuring associations with the drug exposures of interest with residual nephrotoxicity due to previous ART exposure [43]. Furthermore, we may have been better able to detect additive or synergistic toxicities by examining ART regimens within a small number of mutually exclusive categories rather than evaluating drug combinations or interactions between numerous individual drugs. Finally by excluding indinavir, the ART-associated nephrotoxicity that we observed may be more representative of current ART regimens.

The strong association between black race and severe CKD highlights the disproportionate and substantial burden of kidney disease among African Americans, as has previously been documented, particularly in association with advanced kidney disease [37,44]. The present study also identifies an important contribution by hepatitis C to the risk of severe CKD in persons with HIV disease, extending recent associations found with modest eGFR declines and heavy proteinuria among HCV coinfected patients [45–47]. It is possible that other factors associated with past or current injection drug use may confound associations between hepatitis C and CKD.

Consistent with a previous study, we observed a significantly slower rate of eGFR decline on ART [6]. Although eGFR improved with each ART regimen-type, such improvement was significant only in association with tenofovir and a rPI, a regimen-type that was also associated with significantly higher risk of CKD. A possible explanation for these findings may be that tenofovir and a rPI does not adversely affect kidney function in most patients, but may only affect a subset of patients. In support of this, despite the high relative risk of CKD associated with this regimen, CKD developed in less than 6% of patients after 4 years of exposure. Risk factors for tenofovir-associated renal tubular toxicity in previous studies include older age, lower body mass index, and lower eGFR at the start of therapy [17,48,49]. Among all baseline factors, we detected an interaction between ART regimen and race, which was of uncertain significance given the small sample size that warrants further study.

This study was conducted among patients in routine care whose initial ART regimen was not randomly assigned. Thus, differences in baseline characteristics among patients receiving different types of initial ART could contribute to confounding by indication, which has the potential to minimize apparent toxicities associated with tenofovir for example, if patients, who were at greater risk for kidney disease were also less likely to receive this drug. In addition, changes in ART regimens in routine care limit the ability to directly examine associations between drug-exposure and CKD risk. Therefore, we examined CKD risk associated with initial ART regimen using marginal structural logistic regression models to control for confounding by indication and potential bias due to informative censoring that may occur if ART changes were made before eGFR declines fell below event-defining thresholds, resulting in missed CKD events. Thus, this analysis provides more reliable estimates of CKD risk with initial ART than the standard Cox proportional hazards analysis. These models could only control for measured variables that were included in the analysis, however, and residual confounding from unmeasured factors may remain.

It is notable that we observed only 16 cases of severe incident CKD in this cohort with over 10 000 person-years of follow-up on ART. Although this small number of events limited our ability to detect associations with ART, it argues against a general risk of severe nephrotoxicity by any ART regimen-type in the context of usual care with regular toxicity monitoring, given the large sample size and the long follow-up duration of this cohort. Consistent with a recent large study from the Veteran's Administration, we found that tenofovir-containing regimens were not associated with increased risk of more severe CKD defined by eGFR thresholds below 45 or 30 ml/min per 1.73 m^2 [18].

In conclusion, we observed a significantly slower rate of eGFR decline in association with treatment with ART, and lower risk of CKD with higher time-varying CD4 cell count and lower time-varying plasma viral load on ART. Despite these benefits, initial ART regimens that included tenofovir and a rPI were associated with significantly higher risk of CKD compared with a regimen that included a NNRTI without tenofovir, but this developed in less than 6% of patients after 4 years of exposure to such a regimen. Many factors contribute to kidney disease in persons living with HIV infection. These findings suggest durable benefits of ART-associated immunologic and virologic improvements in reducing the risk of kidney disease, while also delineating

contributions by ART-specific toxicities, demographic factors and comorbidities to this important complication.

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Conflicts of interest

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References

1. 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.
2. Kalayjian RC, Franceschini N, Gupta SK, Szczech LA, Mupere E, Bosch RJ, *et al*. **Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease.** *AIDS* 2008; **22**:481–487.
3. Longenecker CT, Scherzer R, Bacchetti P, Lewis CE, Grunfeld C, Shlipak MG. **HIV viremia and changes in kidney function.** *AIDS* 2009; **23**:1089–1096.
4. Peters PJ, Moore DM, Mermin J, Brooks JT, Downing R, Were W, *et al*. **Antiretroviral therapy improves renal function among HIV-infected Ugandans.** *Kidney Int* 2008; **74**:925–929.
5. Reid A, Stohr W, Walker AS, Williams IG, Kityo C, Hughes P, *et al*. **Severe renal dysfunction and risk factors associated with renal impairment in HIV-infected adults in Africa initiating antiretroviral therapy.** *Clin Infect Dis* 2008; **46**:1271–1281.
6. Choi AI, Shlipak MG, Hunt PW, Martin JN, Deeks SG. **HIV-infected persons continue to lose kidney function despite successful antiretroviral therapy.** *AIDS* 2009; **23**:2143–2149.
7. El-Sadr WM, Grund B, Neuhaus J, Babiker A, Cohen CJ, Darbyshire J, *et al*. **Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving episodic therapy: a randomized trial.** *Ann Intern Med* 2008; **149**:289–299.
8. Choi A, Scherzer R, Bacchetti P, Tien PC, Saag MS, Gibert CL, *et al*. **Cystatin C, albuminuria, and 5-year all-cause mortality in HIV-infected persons.** *Am J Kidney Dis* 2010; **56**:872–882.
9. George E, Lucas GM, Nadkarni GN, Fine DM, Moore R, Atta MG. **Kidney function and the risk of cardiovascular events in HIV-1-infected patients.** *AIDS* 2010; **24**:387–394.
10. 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.
11. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, *et al*. **Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV.** *N Engl J Med* 2006; **354**:251–260.
12. Winston A, Amin J, Mallon P, Marriott D, Carr A, Cooper DA, *et al*. **Minor changes in calculated creatinine clearance and anion-gap are associated with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy.** *HIV Med* 2006; **7**:105–111.
13. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, *et al*. **The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years.** *AIDS* 2007; **21**:1273–1281.
14. Young B, Buchacz K, Baker RK, Moorman AC, Wood KC, Chmiel J, *et al*. **Renal function in tenofovir-exposed and tenofovir-unexposed patients receiving highly active antiretroviral therapy in the HIV outpatient study.** *J Int Assoc Physicians AIDS Care (Chic)* 2007; **6**:178–187.
15. Kinai E, Hanabusa H. **Progressive renal tubular dysfunction associated with long-term use of tenofovir DF.** *AIDS Res Hum Retroviruses* 2009; **25**:387–394.
16. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. **Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients.** *Clin Infect Dis* 2010; **51**:496–505.
17. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, *et al*. **Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients.** *AIDS* 2010; **24**:1667–1678.
18. Scherzer R, Estrella M, Li Y, Deeks SG, Grunfeld C, Shlipak MG. **Association of tenofovir exposure with kidney disease risk in HIV infection.** *AIDS* 2012; **26**:867–875.
19. Brewster UC, Perazella MA. **Acute interstitial nephritis associated with atazanavir, a new protease inhibitor.** *Am J Kidney Dis* 2004; **44**:e81–e84.
20. Goicoechea M, Liu S, Best B, Sun S, Jain S, Kemper C, *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.
21. Gallant JE, Moore RD. **Renal function with use of a tenofovir-containing initial antiretroviral regimen.** *AIDS* 2009; **23**:1971–1975.
22. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, *et al*. **Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1: a randomized trial.** *Ann Intern Med* 2011; **154**:445–456.
23. Quiros-Roldan E, Amadasi S, Paraninfo G, Izzo I, Allegri R, Motta D, *et al*. **The impact of gender and anchor drugs on TDF renal toxicity.** *J Acquir Immune Defic Syndr* 2010; **55**:e11–e12.
24. Crane HM, Kestenbaum B, Harrington RD, Kitahata MM. **Amprenavir and didanosine are associated with declining kidney function among patients receiving tenofovir.** *AIDS* 2007; **21**:1431–1439.
25. Kitahata MM, Rodriguez B, Haubrich R, Boswell S, Mathews WC, Lederman MM, *et al*. **Cohort profile: the Centers for AIDS Research Network of Integrated Clinical Systems.** *Int J Epidemiol* 2008; **37**:948–955.
26. Aberg JA, Kaplan JE, Libman H, Emmanuel P, Anderson JR, Stone VE, *et al*. **Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America.** *Clin Infect Dis* 2009; **49**:651–681.
27. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al*. **A new equation to estimate glomerular filtration rate.** *Ann Intern Med* 2009; **150**:604–612.
28. Eknoyan G, Levin NW. **K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.** *Am J Kidney Dis* 2002; **39**:S1–S266.

29. Levey AS, de Jong PE, Coresh J, Nahas ME, Astor BC, Matsushita K, *et al*. **The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report.** *Kidney Int* 2011; **80**:17–28.
30. Lee BK, Lessler J, Stuart EA. **Improving propensity score weighting using machine learning.** *Stat Med* 2010; **29**:337–346.
31. Cain LE, Cole SR. **Inverse probability-of-censoring weights for the correction of time-varying noncompliance in the effect of randomized highly active antiretroviral therapy on incident AIDS or death.** *Stat Med* 2009; **28**:1725–1738.
32. Hernan MA, Brumback B, Robins JM. **Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men.** *Epidemiology* 2000; **11**:561–570.
33. Gooley TA, Leisenring W, Crowley J, Storer BE. **Estimation of failure probabilities in the presence of competing risks: new representations of old estimators.** *Stat Med* 1999; **18**:695–706.
34. Cosgrove CJ, Abu-Alfa AK, Perazella MA. **Observations on HIV-associated renal disease in the era of highly active antiretroviral therapy.** *Am J Med Sci* 2002; **323**:102–106.
35. Szczech LA, Edwards LJ, Sanders LL, van der Horst C, Bartlett JA, Heald AE, *et al*. **Protease inhibitors are associated with a slowed progression of HIV-related renal diseases.** *Clin Nephrol* 2002; **57**:336–341.
36. Szczech LA, Gupta SK, Habash R, Guasch A, Kalayjian R, Appel R, *et al*. **The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection.** *Kidney Int* 2004; **66**:1145–1152.
37. Lucas GM, Lau B, Atta MG, Fine DM, Keruly J, Moore RD. **Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races.** *J Infect Dis* 2008; **197**:1548–1557.
38. Achhra AC, Amin J, Law MG, Emery S, Gerstoft J, Gordin FM, *et al*. **Immunodeficiency and the risk of serious clinical endpoints in a well studied cohort of treated HIV-infected patients.** *AIDS* 2010; **24**:1877–1886.
39. Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, MacArthur RD, *et al*. **CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection.** *AIDS* 2008; **22**:841–848.
40. Tong L, Phan TK, Robinson KL, Babusis D, Strab R, Bhoopathy S, *et al*. **Effects of human immunodeficiency virus protease inhibitors on the intestinal absorption of tenofovir disoproxil fumarate *in vitro*.** *Antimicrob Agents Chemother* 2007; **51**:3498–3504.
41. Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. **Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir.** *J Acquir Immune Defic Syndr* 2006; **43**:278–283.
42. Antoniou T, Raboud J, Chirhin S, Yoong D, Govan V, Gough K, *et al*. **Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study.** *HIV Med* 2005; **6**:284–290.
43. Wever K, van Agtmael MA, Carr A. **Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men.** *J Acquir Immune Defic Syndr* 2010; **55**:78–81.
44. Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. **The impact of HIV on chronic kidney disease outcomes.** *Kidney Int* 2007; **72**:1380–1387.
45. Wyatt CM, Malvestutto C, Coca SG, Klotman PE, Parikh CR. **The impact of hepatitis C virus coinfection on HIV-related kidney disease: a systematic review and meta-analysis.** *AIDS* 2008; **22**:1799–1807.
46. Gupta SK, Komarow L, Gulick RM, Pollard RB, Robbins GK, Franceschini N, *et al*. **Proteinuria, creatinine clearance, and immune activation in antiretroviral-naive HIV-infected subjects.** *J Infect Dis* 2009; **200**:614–618.
47. Fischer MJ, Wyatt CM, Gordon K, Gibert CL, Brown ST, Rimland D, *et al*. **Hepatitis C and the risk of kidney disease and mortality in veterans with HIV.** *J Acquir Immune Defic Syndr* 2010; **53**:222–226.
48. Dauchy FA, Lawson-Ayayi S, de La Faille R, Bonnet F, Rigothier C, Mehsen N, *et al*. **Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy.** *Kidney Int* 2011; **80**:302–309.
49. Rodriguez-Novoa S, Labarga P, Soriano V, Egan D, Albalater M, Morello J, *et al*. **Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study.** *Clin Infect Dis* 2009; **48**:e108–116.