MAJOR ARTICLE

Greater Tenofovir-Associated Renal Function Decline with Protease Inhibitor–Based versus Nonnucleoside Reverse-Transcriptase Inhibitor–Based Therapy

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(See the editorial commentary by Szczech, on pages 7–9.)

Background. Plasma concentrations of tenofovir increase when the drug is coadministered with some ritonavir-boosted protease inhibitors (PI/r). We hypothesized that tenofovir disoproxil fumarate (TDF)–treated patients taking PI/r-based regimens would have a greater decline in renal function than patients receiving nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based therapy.

Methods. We compared the estimated decline in renal function among 146 human immunodeficiency virus type 1 (HIV-1)–infected patients receiving a TDF+PI/r- ($n = 51$), TDF+NNRTI- ($n = 29$), or non–TDF-containing ($n = 66$) regimen. Plasma tenofovir concentrations were measured at study week 2, and rates of creatinine clearance (CrCl) were estimated using the Cockcroft-Gault (C-G) and Modification of Diet in Renal Disease (MDRD) equations. Mixed-effects models were used to analyze regimen type and tenofovir concentration as predictors of change in CrCl from baseline to weeks 24 and 48.

Results. Decreases in C-G estimates of CrCl were not significantly different among the 3 groups during the first 24 weeks of therapy. However, in adjusted analyses, patients receiving TDF+PI/r had a greater rate of decline in CrCl than did the TDF+NNRTI group (for C-G, −13.9 vs. −6.2 mL/min/year [$P = .03$]; for MDRD, −14.7 vs. −4.5 mL/min/1.73 m^2/year [$P = .02$]). Among TDF-treated patients, tenofovir plasma concentration was not associated with CrCl over time.

Conclusions. Treatment with TDF and PI/r was associated with greater declines in renal function over 48 weeks compared with TDF+NNRTI-based regimens.

Tenofovir disoproxil fumarate (TDF) is an oral prodrug of tenofovir and, like cidofovir and adefovir, is an acyclic nucleoside phosphonate. Tenofovir is eliminated by renal clearance, largely by glomerular filtration, with 20%–30% being actively transported into renal proximal tubule cells by organic anion transporter (OAT)–1 [1]. Once inside the cell, tenofovir is excreted into the urine by multidrug resistance protein (MRP)–2 [2, 3] and MRP-4 [4]. Controlled clinical studies of TDF used in efavirenz-based regimens have demonstrated low rates of renal toxicity [5, 6]. However, conflicting data regarding an increased incidence of TDF-associated nephrotoxicity in combination with ritonavir-boosted protease inhibitor (PI/r)–based therapy have been reported [7–9].

Some PI/r-based therapies can increase plasma exposure of tenofovir by ~20%–30% [10, 11]. In animal studies, high doses of TDF for prolonged periods led to a Fanconi-like syndrome with reduced renal tenofovir clearance [12]. At present, the mechanism for increased tenofovir exposure during PI/r coadministration is unclear. Ray et al. [13] observed in vitro that TDF is a substrate for P glycoprotein and that PI/r inhibition of this

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transporter in enterocytes may increase absorption and systemic exposure of tenofovir. Alternatively, in vivo studies in HIV-infected patients have demonstrated reduced tenofovir renal clearance among patients receiving a PI/r than among non–PI-treated patients [14, 15], suggesting that impaired renal excretion leads to increased tenofovir plasma concentrations.

The objective of the present study was to investigate the relationship between PI/r coadministration with TDF and changes in estimated renal function. Comparator groups included HIV-infected patients receiving TDF and nonnucleoside reverse-transcriptase inhibitor (NNRTI)– and non–TDF-containing treatment regimens. In addition, steady-state (week 2) tenofovir plasma exposures were determined to evaluate the association between tenofovir concentration and longitudinal changes in renal function.

METHODS

Study population. Subjects included in this analysis were identified from California Collaborative Treatment Group (CCTG) 578, a prospective, randomized clinical trial of therapeutic drug monitoring of antiretroviral therapy [16]. In this study, patients were recruited from 5 HIV outpatient clinics in California on the basis of the need to initiate a new HIV regimen and to improve medication adherence behaviors, as determined by the health care provider and/or the patient's self-description. Subjects were antiretroviral naive or experienced and had baseline detectable plasma HIV-1 RNA loads regardless of whether they were not currently receiving therapy or experiencing treatment failure with their current regimen. All patients initiated a new PI/r- or NNRTI-based regimen at study entry. Subjects were eligible for the present analysis if they had serum creatinine values available at baseline and at week 48 of therapy. Because the renal effects of tenofovir were hypothesized to be dependent on exposure, TDF-treated subjects were included if they received continuous TDF treatment for at least 40 weeks; otherwise, all other subjects receiving a PI/r- or NNTRI-based therapy and not receiving TDF were analyzed. The duration of antiretroviral therapy among the 3 treatment groups was comparable. Appropriate written informed consent was obtained from all study participants.

Measurements. Rates of creatinine clearance (CrCl) were estimated using the Cockcroft-Gault (C-G) equation [17] and the unabbreviated Modification of Diet in Renal Disease (MDRD) equation (equation 7) [18]. The subject's ideal body weight was used in the C-G estimations. In CCTG 578, serum creatinine levels were routinely monitored (baseline and weeks 2, 6, 12, 24, 32, 40, and 48) and measured at a central laboratory (Quest Diagnostics). Estimates of renal function were based on creatinine values obtained at weeks 24 and 48; however, if serum creatinine laboratory values were not available from these time points, values at weeks 32 and 40 were used, respectively. Tenofovir concentrations were measured at the Norris Cancer Center PharmacoAnalytical Laboratory in stored plasma samples collected before and 2 and 4 h after a witnessed medication dose at study week 2, by a validated liquid-chromatography mass-spectroscopy method. The calibration curve range for tenofovir in human plasma was 10–1000 ng/mL, with a lower limit of quantification of 10 ng/mL. The assay was linear over this range ($r^2 > 0.99$) and demonstrated excellent interday accuracy and precision. Individual tenofovir pharmacokinetic parameters, including tenofovir maximum concentration (C_{max}), minimum concentration (C_{min}), and oral clearance (CL/F), were determined for each subject by use of the POSTHOC subroutine in the computer program NONMEM (version V.1; Globomax). A 2-compartmental model and initial population pharmacokinetic parameter estimates from a published population pharmacokinetic study were used for the base population model without covariates [15].

Statistics. Linear mixed-effects models [19, 20] were used to study the relationship between HIV treatment regimen and CrCl over multiple time points (at baseline, week 24, and week 48). The primary fixed-effects covariates in the models were regimen type (TDF+PI/r based vs. TDF+NNRTI based or non-TDF based), time, and the interaction term "regimen type × time." The intercept term was allowed to vary across individuals and was treated as the only random effect in the model. The interaction term in the model represented the difference in the slopes of change in CrCl over time between the different treatment groups. Other potential confounders—such as age, race (white vs. nonwhite), sex, baseline $CD4^+$ T cell count, baseline HIV-1 RNA load, and treatment history (experienced and receiving therapy, experienced and not receiving therapy, and naive)—were included in the model on the basis of clinical considerations. The influence of these covariates on CrCl over time was studied both univariately and in the multivariate mixed-effects model. Sensitivity analysis and model diagnostics were performed under different mixed-effects modeling assumptions, to validate the results.

We also used mixed-effects models to study the relationship between tenofovir plasma exposure at week 2 (C_{min}, C_{max}, or CL/F) and CrCl over time. In these models, plasma exposure, time, and the interaction term "plasma exposure × time" were included as the main fixed effects, and intercept was the only random effect. Logistic regression models evaluated baseline factors as predictors of a significant decline in CrCl (defined as a >15% decrease from baseline) among TDF-treated patients. Student's *t* tests were used for comparisons of change in CrCl between treatment groups at week 24 and 48. Statistical analysis was performed using R (version 2.4.1).

RESULTS

Patient characteristics. One-hundred ninety-nine patients participated in the parent study, of whom 48 who did not initiate or

Table 1. Baseline demographics and antiretroviral regimen.

Characteristic	TDF-containing regimen		Non–TDF-containing regimen ($n = 66$)	P
	PI/r ($n = 51$)	NNRTI ($n = 29$)		
Age, years	40.6 ± 7.3	39.7 ± 7.6	38.8 ± 8.3	.42
Male, %	76	86	80	.59
Race, %				.85
White	37	45	29	
Black	12	10	17	
Hispanic	45	45	47	
Asian	2	0	5	
Other	4	0	3	
Treatment history, %				<.01
Naive	10	38	53	
Experienced and receiving therapy	45	48	23	
Experienced and not receiving therapy	45	14	24	
$CD4^+$ T cell count, cells/mm^3	220 ± 170	186 ± 158	184 ± 144	.43
HIV RNA-1 load, log_{10} copies/mL	5.00 ± 0.69	5.37 ± 0.49	5.23 ± 0.68	.04
Creatinine clearance				
Cockcroft-Gault estimation, mL/min	111 ± 28	108 ± 22	102 ± 30	.17
MDRD estimation, mL/min/1.73 m^2	110 ± 26	106 ± 23	109 ± 28	.79
PI, no. (%) of subjects receiving				
Lopinavir-ritonavir	38 (75)	NA	26 (39)	ND
Amprenavir-ritonavir	5 (10)	NA	1 (2)	ND
Atazanavir-ritonavir	4 (8)	NA	1 (2)	ND
Saquinavir-ritonavir	3 (6)	NA	3 (5)	ND
Indinavir-ritonavir	3 (6)	NA	0	ND
NNRTI, no. (%) of subjects receiving				
Efavirenz	4 (8)	23 (79)	24 (36)	ND
Nevirapine	NA	6 (21)	11 (17)	ND
NRTI, no. (%) of subjects receiving				
Zidovudine	20 (39)	2 (7)	52 (79)	ND
Lamivudine	32 (63)	13 (45)	58 (88)	ND
Emtricitabine	3 (6)	5 (17)	0	ND
Abacavir	21 (41)	6 (21)	28 (42)	ND
Didanosine	14 (27)	8 (28)	9 (14)	ND
Stavudine	1 (2)	1 (3)	8 (12)	ND

NOTE. Data are mean ± SD values, unless otherwise indicated. Analysis of variance and Fisher's exact tests were used to compare characteristics between treatment groups. MDRD, Modification of Diet in Renal Disease; NA, not applicable; ND, not done; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir disoproxil fumarate.

discontinued TDF before week 48, 3 who received TDF without a PI/r or an NNRTI, and 2 who received TDF with a baseline CrCl rate <50 mL/min were excluded from this analysis. Of the remaining 146 patients, 51 received a TDF+PI/r-, 29 received a TDF+NNRTI-, and 66 received a non–TDF-containing HIV treatment regimen (table 1). Of note, 4 patients treated with TDF and both an NNRTI and PI/r were assigned to the PI/r group. No significant differences were noted between treatment groups with respect to age, sex, race, or baseline $CD4^+$ T cell count. Patients receiving TDF+NNRTI were more often treatment naive and had higher baseline HIV-1 RNA loads than did patients receiving a PI/r. The mean baseline renal function was within the normal range and was similar between treatment groups by either estimate of CrCl (C-G range, 102–111 mL/min [$P = .17$]; MDRD range, 106–110 mL/min/1.73 m^2 [$P = .79$]). Most patients in the TDF+PI/r group received lopinavir-ritonavir (75%), whereas efavirenz (79%) was most commonly used in the TDF+NNRTI group. In the non-TDF group, approximately half received a PI/r, and the rest received an NNRTI.

Change in estimated renal function (C-G). In univariate analysis, decreases in C-G estimates of CrCl were not significantly different among the 3 groups during the first 24 weeks of therapy (mean [SE], −7.75 [2.2] for TDF+PI, −4.46 [3.1] for TDF+NNRTI, and −1.14 [2.8] mL/min for non-TDF) (figure 1). After week 48, the TDF+NNRTI and non-TDF groups continued to have similar changes in renal function from baseline

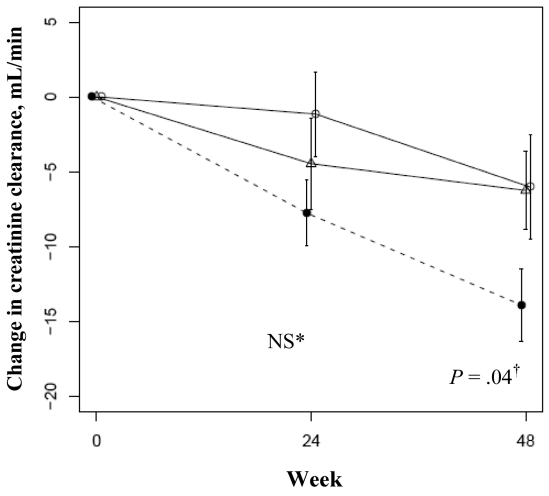

Figure 1. Regimen type and change in renal function. The solid line with white circles represents individuals receiving a non–tenofovir disoproxil fumarate (TDF)–based regimen, the dashed line with black circles represents individuals receiving a TDF plus ritonavir-boosted protease-inhibitor (PI/r)–based regimen, and the solid line with white triangles represents individuals receiving a TDF plus nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based regimen. Student's *t* tests were used for comparisons between regimen types. Errors bars represent SEs. *Comparisons between the TDF+NNRTI group and the TDF+PI/r or non-TDF group. †Comparison between the TDF+NNRTI group and the TDF+PI/r group. NS, nonsignificant.

(mean [SE], −6.24 [2.6] and −6.02 [3.5] mL/min, respectively [$P = .96$]). However, TDF+PI/r-treated patients had greater week 48 declines in CrCl than did patients receiving a TDF+NNRTI-based regimen (mean [SE], −13.9 [2.4] and −6.24 [2.6] mL/min, respectively [$P = .04$]). In addition, increasing age ($P = .001$) and female sex ($P < .001$) were associated with lower baseline CrCl, whereas race, baseline $CD4^+$ T cell count, baseline HIV-1 RNA load, and treatment history were not.

In mixed-effects analysis, patients receiving TDF+PI/r had an increased rate of decline in CrCl compared with the TDF+NNRTI group over 48 weeks (mean [SE], 7.66 [3.6] mL/min/year [$P = .03$]) (table 2). In addition, baseline CrCl decreased by 1.15 mL/min for every 1 year increase in patient age ($P < .001$), and women had lower baseline CrCl than men (22.3 mL/min lower [$P < .001$]). Compared with patients treated with non–TDF-containing regimens, the TDF+PI/r group also had a greater rate of renal function decline after 48 weeks of therapy (mean [SE], 7.88 [3.73] mL/min/year [$P = .04$]). In this model, age and sex continued to be significantly associated with baseline renal function; in addition, individuals with higher baseline $CD4^+$ T cell counts ($P = .08$) and HIV-1 RNA loads ($P = .09$) trended toward higher initial CrCl.

Change in estimated renal function (MDRD). Repeat mixed-effects analysis using the MDRD equation yielded results similar to those of the C-G estimation (table 2). In this analysis, the TDF+PI/r group had a greater rate of renal function decline than did both the TDF+NNRTI (mean [SE], 10.15 [4.23] mL/min/1.73 m^2/year [$P = .02$]) and non-TDF groups (mean [SE], 9.92 [4.58] mL/min/1.73 m^2/year [$P = .03$]). Increasing age was also associated with lower initial estimates of CrCl (~1 mL/min/1.73 m^2 decline per year). Also, in the model including non–TDF-treated patients, treatment-experienced patients not receiving therapy at baseline had significantly lower initial CrCl (mean [SE], −11.37 [5.67] mL/min/1.73 m^2 [$P = .05$]) than did antiretroviral-naive patients.

Plasma concentrations of tenofovir. We sought to determine a possible relationship between steady-state (week 2) tenofovir plasma concentrations and subsequent changes in renal function. Patients receiving a PI/r had tenofovir plasma concentrations and oral clearance rates similar to those of NNRTI-treated individuals (C_{max}, 255 vs. 225 ng/mL [$P = .34$]; C_{min}, 76 vs. 63 ng/mL [$P = .18$]; CL/F, 96 vs. 108 L/h [$P = .36$]). In mixed-effects models, after adjustment for age, none of these pharmacokinetic parameters were associated with CrCl over time. Furthermore, no association was found between the week 2 population-predicted individual plasma concentrations of PI/rs or NNRTIs (C_{min} or C_{max}) and CrCl over time (data not shown).

Effect of HIV treatment outcomes on renal function. All 3 treatment groups had persistent, low-level viremia after 48 weeks of therapy. Patients receiving TDF+PI/r-based regimens had significantly greater HIV-1 RNA loads than did TDF+NNRTI-treated patients (mean [SD], 1622 [25] vs. 363 [10] copies/mL [$P = .03$]) but had levels similar to those in non–TDF-treated subjects (mean [SD], 813 [20] copies/mL [$P = .28$]). Importantly, the proportion of subjects with complete viral suppression (HIV-1 RNA load <50 copies/mL) was not significantly different among treatment groups. Furthermore, $CD4^+$ T cell recovery was similar among all 3 treatment groups, and there were no significant differences in mean $CD4^+$ T cell counts at week 48 (mean range, 323–362 cells/mm^3). In separate mixed-effects models, longitudinal changes in $CD4^+$ T cell counts and HIV-1 RNA loads were not associated with CrCl and did not change the effect of treatment group on renal function decline (data not shown).

Increases in body weight may increase serum creatinine levels and decrease estimated kidney function [21]. Over 48 weeks of follow-up, TDF+NNRTI-treated patients had the greatest increase in body weight (mean, 9.1-kg gain), followed by patients receiving non–TDF- (mean, 7.3-kg gain) and TDF+PI/r-based (mean, 0.8-kg gain) regimens. However, in adjusted analysis, these changes in body weight were not associated with the observed differences in CrCl among the treatment groups (data not shown).

Table 2. Multivariate analysis of regimen type as a predictor of renal function decline.

	TDF+PI/r vs. TDF+NNRTI (n = 77)		TDF+PI/r vs. non-TDF (n = 101)	
Factor	CrCl, mean (SE)	P	CrCl, mean (SE)	P
	C-G estimation, mL/min			
PI/r-containing regimen × time[a]	−7.66 (3.6)	.03	−7.88 (3.73)	.04
Age[b]	−1.15 (0.33)	<.01	−1.60 (0.25)	<.01
Male sex	22.32 (5.98)	<.01	20.51 (5.03)	<.01
Baseline CD4$^+$ T cell count[c]	ND	ND	2.38 (1.36)	.08
Baseline HIV-1 RNA load[d]	ND	ND	5.40 (3.18)	.09
	MDRD estimation, mL/min/1.73 m^2			
PI/r-containing regimen × time[a]	−10.15 (4.23)	.02	−9.92 (4.58)	.03
Age[b]	−0.83 (0.33)	.01	−1.16 (0.27)	<.01
Nonwhite race	13.76 (4.89)	<.01	6.40 (4.31)	.14
Naive vs. experienced and receiving therapy	ND	ND	−5.12 (5.68)	.37
Naive vs. experienced and not receiving therapy	ND	ND	−11.37 (5.67)	.05

NOTE. Mixed-effects models were used for these analyses. The outcome variable was rate of creatinine clearance (CrCl) at baseline, week 24, and week 48, estimated by the Cockcroft-Gault (C-G) or Modification of Diet in Renal Disease (MDRD) equation, for each model. Covariates were included in the multivariate model if significant at $\alpha = 0.25$ in univariate analysis. ND, not done; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir disoproxil fumarate.

[a] Relative difference in change in CrCl over 48 weeks between a TDF+PI/r-containing regimen and a TDF+NNRTI- or non–TDF-containing regimen.

[b] Change in baseline CrCl per 1-year increase.

[c] Change in baseline CrCl per 100 CD4$^+$ T cells/mm^3 increase.

[d] Change in baseline CrCl per 1.0 HIV RNA $\log_{10}$ copies/mL increase.

Predictors of significant renal function decline. Thirty-four percent (26/77) of patients receiving TDF developed significant renal function decline (defined as a >15% decrease in C-G–estimated CrCl) after 48 weeks of therapy. There was no statistically significant association between age, sex, race (white vs. nonwhite), baseline CrCl, or week 2 tenofovir plasma exposures and 1-year renal function decline. However, in adjusted analysis of baseline HIV-1 loads, the odds of developing significant renal function decline among TDF-treated patients was 3.7 times higher for subjects receiving concomitant PI/r versus those receiving NNRTI-based therapy ($P = .04$).

DISCUSSION

Renal impairment is a common problem among HIV-infected patients, and the uncertainty surrounding TDF's potential for renal toxicity is a current therapeutic dilemma. Of the 146 subjects in the present longitudinal study, those receiving concurrent TDF+PI/r treatment had greater reductions in CrCl than did patients taking TDF+NNRTI- or non–TDF-based regimens. Given that some PI/r-based therapies increase systemic tenofovir exposure [10, 11], understanding this mechanism and whether it is due to increased intestinal absorption or decreased renal excretion will have disparate clinical implications. If the cause of the pharmacokinetic drug interaction is within the renal cell itself, then a reduction in the dose of TDF would not necessarily decrease the risk of nephrotoxicity with PI/r coadministration.

Ritonavir is a potent inhibitor of MRP-2 [22]. Although in vitro studies do not agree on the role played by MRP-2 in the cellular transport of tenofovir [2, 4], experiments in animal models using wild-type and MRP-2–deficient (GY/TR$^-$) rats confirm that tenofovir is transported by MRP-2 [3]. Furthermore, recent clinical data demonstrate that genetic polymorphisms in MRP-2 promoter and/or coding regions are associated with differences in urinary tenofovir excretion [23] and the probability of developing TDF-associated renal proximal tubulopathy [24] in HIV-infected patients.

Impaired renal tenofovir excretion by PI/r-based therapies would explain 2 observations. First, increased rates of renal insufficiency have not been observed in large randomized trials of TDF in combination with efavirenz [5, 6]. NNRTIs do not inhibit renal transporters [25]. Coadministration of this drug class would not impair renal clearance, with consequent higher intracellular tenofovir accumulation and cytotoxicity. Therefore, the risk of renal impairment with this regimen combination should be low. Second, we found no association between steady-state tenofovir plasma exposure and change in CrCl over time—even after adjusting for baseline renal function. It is possible that intracellular tenofovir and/or its phosphorylated anabolites are linked more strongly with renal cell cytotoxicity and that plasma tenofovir levels may correlate poorly with these concentrations.

Differences in outcome between our study and other observational studies of TDF- and PI/r-treated patients can be attributed to differences in cohort selection. The HIV Outpatient Study (HOPS) assessed the effect of TDF in combination with lopinavir-ritonavir or atazanavir-ritonavir ($n = 99$) versus TDF+NNRTI or other PI-based regimens ($n = 210$) on change in renal function [7]. After 12 months of follow-up, the groups had no significant differences with respect to CrCl decline (−5.1 vs. −2.8 mL/min [$P = .51$]). The smaller observed change in renal function among these PI/r-treated patients may have been the result of differences in patient characteristics. The HOPS cohort included only antiretroviral-naive patients with less-advanced HIV disease (median $CD4^+$ T cell count, 352–427 cells/mm^3), compared with those in the present study (median $CD4^+$ T cell count, 184–220 cells/mm^3). Moreover, the comparator group contained both TDF- and other PI+TDF-treated patients, which may have decreased renal function in this study arm, reducing the size of the effect and the power to detect a difference between treatment groups. Indeed, Winston et al. [9] did observe significant changes in renal function among antiretroviral-naive patients with high $CD4^+$ T cell counts (mean $CD4^+$ T cell count, 381–461 cells/mm^3) receiving either a TDF- ($n = 290$) or non–TDF- ($n = 618$) containing regimen. In the present study, TDF-treated patients (70% with concurrent PI/r) did have significantly greater time-weighted declines in CrCl than did non–TDF-treated patients (−5.6 mL/min vs. 1.26 mL/min [$P = .01$]).

Patients with advanced disease are at increased risk for chronic kidney disease [26] and may be more susceptible to tenofovir-associated renal toxicity. In the Johns Hopkins clinical cohort, composed of individuals with low baseline $CD4^+$ T cell counts (median $CD4^+$ T cell count, 214–220 cells/mm^3), renal function decline between individuals receiving TDF ($n = 344$) versus other nucleoside-based ($n = 314$) regimens was compared [8]. Although only 36% of the TDF-treated patients received concurrent PI/r therapy, this group had significantly greater declines in renal function than did non–TDF-treated patients (−13.3 vs. −7.5 mL/min [$P = .005$]). Of note, the magnitudes of CrCl declines were similar to the changes observed in our study for TDF+PI/r- and non–TDF-treated patients (−13.9 mL/min and −6.0 mL/min, respectively), which may reflect baseline similarities between the study cohorts.

This retrospective analysis had several limitations, most notably that HIV regimens were not randomized at baseline and that significant differences were seen in the proportion of treatment-experienced patients between groups. Patients receiving TDF and NNRTIs were more often treatment naive than were TDF+PI/r-treated individuals (38% vs. 10%). Potentially, treatment-experienced patients may be more predisposed to renal adverse events. However, all groups had similar, normal-range CrCl rates at baseline, and adjusted analyses between TDF+PI/r- and non–TDF-treated patients demonstrated the independent effect of a TDF+PI/r regimen even after adjusting for treatment experience. In addition, tenofovir plasma exposure was measured only after 2 weeks of therapy. This may have been too early to observe the full effects of PI inhibition of MRP-2. Potentially, serial measurements over longer periods may capture interpatient differences in plasma tenofovir concentrations due to MRP-2 inhibition and associate better with change in renal function over time. Furthermore, data on the proportion of subjects with diabetes mellitus, hypertension, proteinuria, and concurrent nephrotoxic medications were not available. Knowing that these potential confounders were not more common in one group than another would have been reassuring.

Differences in HIV disease outcome among treatment groups could have an independent effect on kidney function. The C-G and MDRD equations include variables such as age, sex, race, body weight, blood urea nitrogen level, albumin level, and serum creatinine level as surrogates for muscle mass. Body weight increased to a greater extent in the TDF+NNRTI and non-TDF groups than in the TDF+PI/r group. However, this difference in weight gain represents a conservative bias and provides evidence that the observed increases in estimated CrCl in the TDF+PI/r group were not due to a relative increase in muscle mass. In addition, low $CD4^+$ T cell counts and high HIV-1 RNA loads are considered to be risk factors for chronic kidney disease [26]. Although viral suppression was greater in the TDF+NNRTI group (probably because of the higher proportion of treatment-naive patients in this group), the difference in viral load compared with that in the TDF+PI/r group was small (change in HIV-1 RNA load, 1259 copies/mL) and was likely not clinically relevant, given that $CD4^+$ T cell recovery was similar among the 3 treatment groups.

In conclusion, the present study demonstrated that patients receiving TDF in combination with PI/r-based regimens had greater declines in renal function than did TDF+NNRTI- or non–TDF-treated individuals. Although the magnitude of CrCl decline was relatively small, if it were to continue throughout the life of a patient, it would have serious clinical implications. In our cohort, the only risk factor for significant 1-year renal function decline (>15% decrease from baseline at week 48) among patients initiating TDF-based therapy was concurrent use of a PI/r-containing regimen. We postulate that the mechanism is a drug-drug interaction at the level of renal proximal tubule cell, whereby PI/r-based therapies inhibit tenofovir efflux, resulting in greater intracellular accumulation. Moreover, genetic polymorphisms in renal tubular transporters may modify this risk [27–29]. Future investigations are needed to identify individuals with polymorphisms for high OAT-1 expression and/or low-functioning MRP-2/4 transporters, because these patients may be at increased risk for renal toxicity.

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