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Estimated Glomerular Filtration Rate Trajectories in HIV-Infected Subjects Treated With Different Ritonavir-Boosted Protease Inhibitors and Tenofovir Disoproxil Fumarate or Abacavir

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Abstract: The aim of the study was to evaluate in human immunodeficiency virus (HIV)-infected patients estimated glomerular filtration rate (eGFR) trajectories during treatment with different protease inhibitors (PIs) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus tenofovir (TDF) or abacavir (ABC) and lamivudine or emtricitabine (xTC).

Retrospective study of patients followed at a single clinical center; all patients who started TDF or ABC for the first time with a NNRTI or lopinavir/r (LPV/r) or atazanavir/r (ATV/r) or darunavir/r (DRV/r), for whom at least 1 eGFR value before the start and during the studied treatment was known, were included in this analysis. eGFR was calculated by means of the CKD-EPI formula. Univariate and multivariate mixed linear model (MLM) was applied to estimate eGFR slope with the considered antiretroviral treatment.

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In the 1658 patients treated with TDF/xTC (aged 43 [37–48] years, with an eGFR of 105 [96; 113] mL/min/1.73 m², 80% males, 92% Caucasians, 10% coinfecting with HCV, 4% with diabetes, 11% with hypertension, 38% naive for antiretroviral therapy (ART), 37% with HIV-RNA <50 copies/mL) the median follow-up was 2.5 (1.2–4.6) years. Their adjusted eGFR slopes (95% CI) were –1.26 (–1.58; –0.95), –0.43 (–1.20; +0.33), –0.86 (–1.28; –0.44), and –0.20 (–0.42; +0.02) mL/min/1.73 m² per year in patients treated with ATV/r, DRV/r, LPV/r, and NNRTI, respectively. Patients receiving ATV/r or LPV/r had a greater adjusted decline in eGFR compared with those receiving NNRTIs (difference –1.06 [–1.44; –0.69] mL/min/1.73 m² per year, *P* < 0.001; and –0.66 [–1.13; –0.20] mL/min/1.73 m² per year, *P* = 0.005, respectively); adjusted eGFR slopes were similar in patients receiving DRV/r and in those receiving NNRTIs. Patients receiving ATV/r had a greater adjusted eGFR decline than those treated with DRV/r (difference –0.83 [–1.65; –0.02] mL/min/1.73 m² per year; *P* = 0.04), but not than those receiving LPV/r; no significant difference was observed in adjusted eGFR slopes between patients receiving DRV/r and those receiving LPV/r. In the 286 patients treated with ABC and lamivudine, eGFR slopes were similar, independent of the PI.

In patients receiving TDF/xTC, eGFR trajectories were small for all regimens and declined less in patients receiving DRV/r or NNRTIs than in those treated with ATV/r or LPV/r.

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Abbreviations: 3TC = lamivudine, ABC = abacavir, AIDS = acquired immune deficiency syndrome, ART = antiretroviral therapy, ATV/r = atazanavir boosted with ritonavir, AUC = area under the curve, BMI = body mass index, CD4 = cluster differentiation 4, CKD = chronic kidney disease, CKD-EPI = chronic kidney disease epidemiology collaboration equation, DRV/r = Darunavir boosted with ritonavir, EFV = Efavirenz, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, FTC = Emtricitabine, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IDD-HSR = Infectious Diseases Department of the San Raffaele Hospital, IQR = interquartile range, LPV/r = Lopinavir boosted with ritonavir, MATE1 = Multidrug and Toxin Extrusion 1, MLM = mixed linear model, MRP4 = multidrug resistance protein 4, NNRTI = non-nucleoside reverse transcriptase inhibitor, P-gp = P-glycoprotein, PI = protease inhibitor, PYFU = person-years of follow-up, RNA = ribonucleic acid, TAF = Tenofovir Alafenamide, TDF = tenofovir disoproxil fumarate, TFV = Tenofovir, xTC = Lamivudine or Emtricitabine.

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a recommended nucleotide reverse transcriptase inhibitor (NRTI) for all

first-line regimens,^{1–4} but patients treated with this drug can experience kidney toxicity. Although kidney toxicity associated with TDF is primarily tubular,^{5–7} patients starting their first-line treatment with regimens including TDF had a larger relative decline in glomerular filtration rate (GFR) than those who received alternative nucleoside analogues.^{8–15} Exposure to TDF was also associated with increased odds^{16–19} and to an higher incidence^{18,20,21} of chronic kidney disease (CKD); however, the loss in eGFR attributable to TDF through 10 years of follow-up was relatively mild in 1 study.²²

Many HIV-infected patients treated with TDF receive this drug along with ritonavir (RTV)-boosted protease inhibitors (PIs/r), which may have renal toxicity themselves and contribute to renal toxicity due to TDF: studies from large international cohorts found an increased risk of CKD associated with the use of either ritonavir-boosted atazanavir (ATV/r) or lopinavir (LPV/r) or unboosted atazanavir, which was independent of TDF use.^{19,20} When patients included in 1 of these cohorts with normal kidney function were followed up, cumulative exposure to TDF, ATV/r, or LPV/r was significantly associated with increasing risk of CKD.²³ However, the risk of developing CKD with the widely used PI/r darunavir/ritonavir (DRV/r) was not specifically investigated in this study.

Cumulatively, data from different studies showed that regimens based on TDF and a PI/r were associated with greater declines in renal function over 48 weeks than those based on TDF in combination with a non-NRTI (NNRTI).^{17,24–31} In particular, in treatment-naïve patients randomized to receive abacavir/lamivudine (ABC/3TC) or TDF/emtricitabine (FTC) with efavirenz (EFV) or ATV/r (A5202 Study), statistically significant improvements from baseline to weeks 48 and 96 in creatinine clearance were found in all treatment arms, except in that of patients treated ATV/r with TDF/FTC.³² Similar findings emerged from a smaller randomized clinical trial.³³

Thus, different PIs/r have different impact on kidney function, which might depend in part upon the association with TDF. However, GFR trajectories in patients treated with different PIs/r or with NNRTIs and different NRTI backbones have not been fully studied.

The primary objective of this study was to evaluate if, in patients treated with a PI/r plus TDF or ABC (and 3TC or FTC), estimated GFR (eGFR) trajectories differ according to the use of different PIs/r in the same regimen. The secondary objective was to compare eGFR trajectories in patients treated with TDF or ABC and different PIs/r to those observed in patients treated with TDF or ABC and NNRTIs.

METHODS

Retrospective cohort study on patients on treatment with TDF or ABC and a PI or a NNRTI, followed at the Infectious Diseases Department of the San Raffaele Scientific Hospital in Milan (Italy) since September 1995 up to September 2014. Data recorded in the database of the Infectious Diseases Department of the San Raffaele (IDD-HSR) in Milan, Italy, were used for the analyses. Briefly, this is an observational database that collects demographic, clinical, therapeutic, and laboratory data of adult subjects receiving primary care for HIV infection, as outpatients or inpatients, at the Infectious Diseases Department of the San Raffaele Scientific Institute in Milan, Italy. At their first visit (in our clinic), subjects provide written informed consent to include their clinical and laboratory data in the IDD-HSR for scientific purposes. Information on prescribed antiretroviral and concomitant drugs (type, dosage, date of start or stop) are

prospectively recorded into the database at each visit by the treating physician and then checked by skilled data managers. For the purpose of the present study, the following demographics and clinical characteristics were retrieved from the database: baseline age, gender, race (ancestry), body mass index (BMI), HIV risk factor, time since HIV diagnosis, coinfection with hepatitis C virus (HCV), presence of diabetes or hypertension, ongoing diuretic therapy, previous diagnosis of acquired immune deficiency syndrome (AIDS), baseline and nadir cluster differentiation 4 (CD4)+ cell count, antiretroviral therapy (ART) history (naïve vs. experienced), time since ART initiation (only for treatment-experienced patients), HIV viral load, eGFR.

Eligible patients were those who started tenofovir (TDF) or abacavir (ABC) in combination with a NNRTI (efavirenz or nevirapine) or lopinavir/r (LPV/r) or atazanavir/r (ATV/r) or darunavir/r (DRV/r), who had a baseline eGFR determination (within 90 days before the start of the considered regimen) and with at least 1 eGFR determination during follow-up, while on this regimen.

Follow-up accrued from the start of TDF/ABC (baseline) up to the stop of any drug of the regimen or lost to follow-up or data freezing (September 2014). For subjects with multiple treatment episodes with TDF or ABC in combination with a NNRTI or LPV/r or ATV/r or DRV/r, the first episode was considered.

For the analysis of eGFR slopes in patients treated with TDF, follow-up after discontinuation of PI or NNRTI or TDF was also considered (the freezing date was always September 2014).

eGFR was calculated using the CKD Epidemiology Collaboration Equation (CKD-EPI).³⁴

A CKD diagnosis was defined as the occurrence of 2 consecutive eGFR determinations <60 mL/min/1.73 m².

Statistical Analysis

eGFR trajectories were estimated during treatment with the studied regimens.

The analyses considered those characteristics that likely determined the choice of the PI/r being considered and thus serving as confounding factors for the outcome of the study. Specifically, we evaluated the following variables: age, gender, race, body mass index, time since HIV diagnosis, baseline CD4+, baseline viral load, hypertension, diabetes, current use of diuretics, nadir CD4+, time since ART initiation, first line versus nonfirst line regimen, HCV coinfection, calendar year of the start of the study regimen.

Results were described as median (interquartile range, IQR) or frequency (%). At univariate analysis, comparisons of subjects' characteristics between antiretroviral treatment groups were performed using the χ^2 /Fisher exact test for categorical variables and by use of the Kruskal–Wallis test or the Wilcoxon rank sum test for continuous variables.

Univariate and multivariate mixed linear models (MLM) with random slope and intercept for each patient were fitted to estimate eGFR changes according to the third drug included in the regimen: 1 NNRTI, ATV/r, DRV/r, LPV/r. Slopes were reported with the corresponding 95% confidence interval. All the baseline characteristics were entered into the multivariate models as potential confounders with the exception of age, gender, race, and creatinine levels as they are already included into the CKD-EPI formula. CD4+ and HIV-RNA were used as time-updated variables.

The incidence rate of CKD development in each study regimen was calculated as number of CKD events per 1000 person-years of follow-up (PYFU). Poisson regression was used for comparisons of incidence rates in the 4 study regimens (ATV/r, DRV/r, LPV/r, and NNRTI).

All analyses were conducted using SAS statistical software version 9.2 (Statistical Analyses System Inc, Cary, NC).

RESULTS

One thousand nine-hundred forty-four patients (1658 treated with TDF and 286 patients treated with ABC), among 4256 on antiretroviral treatment, fulfilled the inclusion criteria. Their baseline characteristics are described in Tables 1 and 2.

Patients Treated With TDF

Among patients treated with TDF ($n = 1658$), 471 (28%) received also ATV/r, 181 (11%) DRV/r, 333 (20%) LPV/r, and 673 (41%) a NNRTI (584 [87%] EFV, 89 [13%] nevirapine); statistically significant differences in baseline characteristics between these 4 groups were observed with regard to age, gender, BMI, years since HIV diagnosis, coinfection with HCV, previous AIDS diagnosis, nadir and current CD4+ count, ART-naïve status, calendar year, HIV-RNA, eGFR; no baseline difference was observed with regard to race, proportion of patients with hypertension or diabetes, on diuretic therapy, and with an eGFR <60 or between 60 and 90 mL/min/1.73 m² (Table 1).

At the end of follow-up (i.e., stop of any drug of the regimen or lost to follow-up or data freezing [September 2014]), the number of patients on study was 1626 (98% of the 1658 initially included: 12 died and 20 were lost to follow-up, after a median [IQR] follow-up of 2.5 [1.2; 4.6] years). The numbers of patients at the end of the observational period in the different groups were: 462/471, 98% (2 deaths and 7 lost to follow-up), after a median (IQR) follow-up of 2.3 (1.1; 4.3) years in the ATV/r group, 325/333, 98% (3 deaths and 5 lost to follow-up), after a median (IQR) follow-up of 1.9 (0.8; 3.5) years in the LPV/r group, 178/181, 98% (2 deaths and 1 lost to follow-up), after a median (IQR) follow-up of 1.6 (0.9; 2.5) years in the DRV/r group, and 661/673, 98% (5 deaths and 7 lost to follow-up), after a median (IQR) follow-up of 3.7 (1.7; 5.4) years in the NNRTI group.

After a median (IQR) overall follow-up of 2.5 (1.2; 4.6) years (2.3 [1.1; 4.3], 1.6 [0.9; 2.5], 1.9 [0.8; 3.5], and 3.7 [1.7; 5.4] years, in patients treated with ATV/r, DRV/r, LPV/r, and NNRTIs, respectively; $P < 0.001$ for all paired comparisons), a modification of any component of the regimen occurred in 1070 (65%) patients (in 347 [74%], 96 [53%], 291 [87%], and 336 [50%] patients treated with ATV/r, DRV/r, LPV/r, and NNRTIs, respectively; $P < 0.001$ for all paired comparisons). Among patients with modifications in the regimen, eGFR at the time of modification was 102 (88; 111) (100 [84; 110], 106 [90; 114], 101 [89; 109], and 104 [92; 112] mL/min/1.73 m² in patients treated with ATV/r, DRV/r, LPV/r, and NNRTI, respectively; $P = 0.001$ and $P = 0.03$ for the comparison of patients treated with ATV/r vs. NNRTI and for patients treated with LPV/r vs. NNRTI, respectively). The number of eGFR determinations per patient during follow-up was 9 (4; 15) (8 [4; 15], 6 [4; 10], 7 [4; 13], and 11 [6; 16] in patients treated with ATV/r, DRV/r, LPV/r and NNRTI, respectively; $P < 0.001$ for every comparison between each PI/r and NNRTIs and $P = 0.003$ for the comparison of patients treated with ATV/r vs. those treated with DRV/r).

Crude eGFR slopes (mL/min/1.73 m² per year) [95% CI] were -0.44 [-0.65 ; -0.24] per 10-years older; $P < 0.0001$ for age and -0.38 [-1.08 ; $+0.32$] vs. -0.94 [-1.13 ; -0.75], $P = 0.136$, for non-white race vs. white race, respectively. Crude eGFR slopes (95% CI) were -1.66 (-2.02 ; -1.30), -1.11 (-1.92 ; -0.31), -1.47 (-1.98 ; -0.96), and -0.39 (-0.65 ; -0.13) mL/min/1.73 m² per year in patients treated with ATV/r, DRV/r, LPV/r, and NNRTI, respectively (ATV/r vs. NNRTI: $P < 0.001$; DRV/r vs. NNRTI: $P = 0.12$; LPV/r vs. NNRTI: $P < 0.001$; no significant differences for other comparisons).

Among the 1658 patients included in this study, 96 (5.8%) had a decline in eGFR $\leq 3\%$ per year with significant differences among treatment groups ($P = 0.014$) (Table 3).

Among subjects with a baseline eGFR ≥ 90 mL/min/1.73 m², CKD developed in 6 (1.3%), none, 3 (0.9%), and 2 (0.3%) patients treated with ATV/r, DRV/r, LPV/r and NNRTI, respectively. Crude incidence rates (95% CI) of CKD were 4.48 (1.61; 8.78), 3.71 (0.7; 9.09), and 0.81 (0.08; 2.32) per 1000-PYFU in patients treated with ATV/r, LPV/r and NNRTI, respectively (LPV/r vs. ATV/r: $P = 0.79$; LPV/r vs. NNRTI: $P = 0.06$; ATV/r vs. NNRTI: $P = 0.02$).

Adjusted eGFR slopes (95% CI) were -1.26 (-1.58 ; -0.95), -0.43 (-1.20 ; $+0.33$), -0.86 (-1.28 ; -0.44), and -0.20 (-0.42 ; $+0.02$) mL/min/1.73 m² per year in patients treated with ATV/r, DRV/r, LPV/r, and NNRTI, respectively, as shown in Table 4, patients treated with ATV/r or LPV/r had a greater adjusted decline in eGFR compared with those treated with NNRTIs ($P < 0.001$ and $P = 0.005$, respectively), while patients receiving DRV/r had an adjusted eGFR slope not statistically different from that observed in those receiving NNRTIs. Patients treated with ATV/r had a greater adjusted eGFR decline than those treated with DRV/r ($P = 0.04$), but not than those treated with LPV/r; no significant statistical difference was observed in adjusted eGFR slopes between patients treated with DRV/r and those treated with LPV/r (Table 4).

The multivariate analysis (Table 5) also showed that eGFR slopes were independently associated with the type of ART ($P < 0.001$), baseline calendar year ($P = 0.01$), hypertension ($P < 0.001$), nadir CD4+ cell count ($P = 0.007$), current CD4+ cell count ($P < 0.001$), and baseline eGFR ($P < 0.001$).

Following discontinuation of only the third drug (393/1070 [24%] subjects: 77 [16%] ATV/r, 47 [26%] DRV/r, 128 [38%] LPV/r, 141 [21%] NNRTI), over a median follow-up of 1.13 (0.45–2.53) years, the mean eGFR increased for patients who discontinued ATV/r [mean slope (95% CI): $+0.57$ (-0.57 ; $+1.71$) mL/min/1.73 m² per year] and among patients who discontinued DRV/r [mean slope (95% CI): $+1.36$ (-0.57 ; $+3.29$) mL/min/1.73 m² per year] while eGFR declines were observed for patients who discontinued either LPV/r [mean slope (95% CI): -0.82 (-1.40 ; -0.24) mL/min/1.73 m² per year] or NNRTI [mean slope (95% CI): -0.50 (-1.36 ; $+0.35$) mL/min/1.73 m² per year].

Following discontinuation of only TDF (244/1070 [23%] subjects: 91 [19%] ATV/r, 20 [11%] DRV/r, 73 [22%] LPV/r, 40 [6%] NNRTI, and 20 patients were lost to follow-up), over a median follow-up of 1.13 (0.45–2.53) years, the mean eGFR increased for patients treated with ATV/r [mean slope (95% CI): $+1.28$ ($+0.32$; $+2.24$) mL/min/1.73 m² per year], among patients treated with DRV/r [mean slope (95% CI): $+6.96$ ($+3.79$; $+10.13$) mL/min/1.73 m² per year] and among patients treated with NNRTI [mean slope (95% CI): $+1.39$ ($+0.14$; $+2.64$) mL/min/1.73 m² per year] while an eGFR decline, not statistically significant, was observed for patients treated with

TABLE 1. Baseline Demographic, Clinical and Laboratory Characteristics of Patients Treated With Tenofovir Plus Emtricitabine or Lamivudine and Either Atazanavir/Ritonavir or Darunavir/Ritonavir or Lopinavir/Ritonavir or a Non-Nucleoside Reverse Transcriptase Inhibitor

	OVERALL (n = 1658)	ATV/r (n = 471)	DRV/r (n = 181)	LPV/r (n = 333)	NNRTI (n = 673)	P Value Overall	P Value ATV/r Vs. DRV/r	P Value ATV/r Vs. NNRTI	P Value DRV/r Vs. NNRTI	P Value LPV/r Vs. NNRTI
Ags, y	43 [37; 48]	43 [38; 47]	39 [34; 46]	43 [37; 47]	43 [37; 49]	0.001*	<0.001†	0.57†	<0.001†	0.39†
Males	1333 [80%]	361 [77%]	157 [87%]	261 [78%]	554 [82%]	0.01†	0.005‡	0.02†	0.17‡	0.14†
White race	1529 [92%]	439 [93%]	163 [90%]	311 [93%]	616 [92%]	0.41†	0.19 †	0.17†	0.55‡	0.32‡
Body mass index, kg/m ²	23.0 [21.1; 25.3]	23.1 [21.1; 25.5]	22.7 [20.9; 24.9]	22.7 [20.8; 25.1]	23.2 [21.2; 25.3]	0.06*	0.09†	0.81†	0.04†	0.04†
HIV risk factor						<0.001†	<0.001†	0.01†	<0.001†	<0.001†
MSM	606 [37%]	156 [33%]	92 [51%]	109 [33%]	249 [37%]					
Heterosexual	314 [19%]	94 [20%]	31 [17%]	65 [20%]	124 [19%]					
IVDU	259 [16%]	89 [19%]	11 [6%]	77 [23%]	82 [12%]					
Other/unknown	479 [28%]	132 [28%]	47 [26%]	82 [24%]	218 [32%]					
Years since HIV diagnosis	7.9 [2.3; 15.2]	11.2 [3.9; 17.1]	2.1 [0.2; 6.6]	9.0 [2.0; 16.2]	7.5 [2.9; 13.9]	<0.001*	<0.001†	<0.001†	<0.001†	0.4†
Anti HCV Ab						<0.001†	<0.001†	0.06†	<0.001†	<0.001†
Positive	160 [10%]	54 [12%]	9 [5%]	47 [14%]	50 [7%]					
Negative	860 [52%]	236 [50%]	135 [75%]	136 [41%]	353 [53%]					
Unknown	638 [38%]	181 [38%]	37 [20%]	150 [45%]	270 [40%]					
Diabetes	71 [4%]	24 [5%]	4 [2%]	13 [4%]	30 [5%]	0.42†	0.13†	0.67†	0.2‡	0.74‡
Hypertension	188 [11%]	60 [13%]	17 [9%]	31 [9%]	80 [12%]	0.36†	0.27†	0.71†	0.42‡	0.24‡
Diuretic therapy	33 [2%]	13 [3%]	1 [1%]	5 [2%]	14 [2%]	0.28†	0.12†	0.55‡	0.17‡	0.62‡
Previous AIDS diagnosis	259 [16%]	72 [15%]	20 [11%]	75 [23%]	92 [14%]	0.001†	0.21†	0.44†	0.38‡	0.001†
CD4+ nadir (cells/ μ L)	247 [129; 340]	242 [132; 339]	255 [91; 360]	211 [81; 296]	266 [166; 354]	<0.001*	0.92†	0.02†	0.17†	<0.001†
ART-naive	622 [38%]	139 [30%]	141 [78%]	108 [32%]	234 [35%]	<0.001†	<0.001†	0.06†	<0.001†	0.48‡
Calendar year	2009 [2007; 2010]	2009 [2007; 2010]	2011 [2011; 2012]	2008 [2007; 2009]	2009 [2007; 2010]	<0.001*	<0.001†	0.5†	<0.001†	<0.001†
Years since ART initiation	9.0 [5.0; 12.2]	9.9 [6.8; 12.9]	7.7 [2.4; 13.7]	8.6 [3.5; 12.0]	8.6 [4.8; 11.7]	<0.001*	0.15†	<0.001†	0.81†	0.91†
(only treatment-experienced patients)										
CD4+ (cells/ μ L)	356 [247; 527]	350 [248; 493]	300 [116; 397]	308 [171; 456]	410 [289; 615]	<0.001*	<0.001†	<0.001†	<0.001†	<0.001†
HIV-RNA (log ₁₀ copies/mL)	3.81 [1.69; 4.85]	3.90 [1.69; 4.79]	4.66 [3.95; 5.26]	3.83 [1.69; 4.98]	2.68 [1.69; 4.55]	<0.001*	<0.001†	<0.001†	<0.001†	<0.001†
HIV-RNA <50 copies/mL	606 [37%]	146 [31%]	18 [10%]	111 [33%]	331 [49%]	<0.001†	<0.001†	<0.001†	<0.001†	<0.001†
eGFR (mL/min/1.73 m ²)	105 [96; 113]	105 [96; 112]	108 [98; 116]	106 [96; 113]	105 [95; 112]	0.02*	0.006†	0.72†	0.003†	0.32†
eGFR <60 mL/min/1.73 m ²	5 [0.3%]	1 [0.2%]	0	3 [0.9%]	1 [0.2%]	0.16†	0.99†	0.99†	0.99†	0.11†
eGFR between 60 and 90 mL/min/1.73 m ²	253 [15%]	65 [14%]	28 (16%)	49 [15%]	111 [17%]	0.64‡	0.61†	0.24‡	0.82‡	0.52‡

ART = antiretroviral therapy, ATV/r = atazanavir/ritonavir, CD4 = cluster differentiation 4, DRV/r = darunavir/ritonavir, eGFR = estimated glomerular filtration rate, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IVDU = intravenous drug user, LPV/r = lopinavir/ritonavir, MSM = man who have sex with man, NNRTI = non-nucleoside reverse transcriptase inhibitor, RNA = ribonucleic acid.
 *Kruskal–Wallis test.
 †Wilcoxon rank sum test.
 ‡ χ^2 /Fisher exact test.

TABLE 2. Baseline Demographic, Clinical and Laboratory Characteristics of Patients Treated With Abacavir Plus Lamivudine and Either Atazanavir/Ritonavir or Darunavir/Ritonavir or Lopinavir/Ritonavir or a Non-Nucleoside Reverse Transcriptase Inhibitor

	OVERALL (n = 286)	ATV/r (n = 90)	DRV/r (n = 25)	LPV/r (n = 55)	NNRTI (n = 116)	P Value		P Value		P Value	
						Overall	Vs. DRV/r	ATV/r Vs. NNRTI	DRV/r Vs. NNRTI	ATV/r Vs. NNRTI	DRV/r Vs. NNRTI
Age, y	45 [39; 50]	42 [38; 50]	42 [36; 47]	46 [40; 50]	46 [39; 51]	0.08*	0.33†	0.09†	0.03†	0.7†	0.7†
Males	217 [76%]	72 [80%]	21 [84%]	44 [80%]	80 [69%]	0.15†	0.77†	0.08†	0.15†	0.14†	0.14†
White race	277 [97%]	85 [94%]	25 [100%]	53 [96%]	114 [98%]	0.34†	0.58†	0.24†	0.99†	0.59†	0.59†
Body mass index, kg/m ²	24.8 [22.6; 27.2]	25.2 [22.9; 28.0]	23.1 [21.5; 25.9]	25.5 [22.5; 28.1]	24.5 [22.5; 26.8]	0.05*	0.007†	0.23†	0.05†	0.38†	0.38†
HIV risk factor						<0.001†	0.03†	0.04†	0.01†	<0.001†	<0.001†
MSM	95 [33%]	25 [28%]	15 [60%]	23 [42%]	32 [28%]						
Hetero	74 [26%]	21 [23%]	3 [12%]	11 [20%]	39 [34%]						
IVDU	40 [14%]	16 [18%]	2 [8%]	15 [27%]	7 [6%]						
Other/unknown	77 [27%]	28 [31%]	5 [20%]	6 [11%]	28 [32%]						
Years since HIV diagnosis	10.4 [3.6; 16.3]	10.7 [2.6; 18.6]	7.2 [0.7; 18.8]	11.4 [5.7; 18.6]	10.1 [5.6; 14.6]	0.53†	0.53†	0.83†	0.38†	0.22†	0.22†
Ab-anti HCV						0.61†	0.63†	0.26†	0.54†	0.66†	0.66†
Positive	25 [9%]	11 [12%]	2 [8%]	5 [9%]	7 [6%]						
Negative	166 [58%]	52 [58%]	17 [68%]	29 [53%]	68 [59%]						
Unknown	95 [33%]	27 [30%]	6 [24%]	21 [38%]	41 [35%]						
Diabetes	16 [6%]	6 [7%]	0	3 [6%]	7 [6%]	0.63†	0.33†	0.99†	.35†	0.99†	0.99†
Hypertension	44 [15%]	11 [12%]	2 [8%]	7 [13%]	24 [21%]	0.21†	0.73†	0.13†	.16†	0.28†	0.28†
Diuretic therapy	6 [2%]	0	0	1 [2%]	5 [4%]	0.15†	0.99†	0.06†	.58†	0.66†	0.66†
Previous AIDS diagnosis	49 [17%]	13 [14%]	1 [4%]	19 [35%]	16 [14%]	0.001†	0.29†	0.99†	0.31†	0.002†	0.002†
Nadir CD4+ (cells/ μ L)	247 [119; 338]	267 [154; 338]	252 [171; 373]	136 [54; 253]	258 [158; 377]	0.01*	0.74†	0.7†	0.97†	<0.001†	<0.001†
ART-naive	64 [22%]	26 [29%]	14 [56%]	8 [15%]	16 [14%]	<0.001†	0.02†	0.009†	<0.001†	0.99†	0.99†
Calendar year	2008 [2006; 2011]	2008 [2006; 2011]	2012 [2011; 2012]	2007 [2006; 2008]	2008 [2006; 2011]	<0.001*	<0.001†	0.84†	<0.001†	0.12†	0.12†
Years since ART initiation (only treatment-experienced patients)	9.9 [6.0; 13.1]	11.8 [7.4; 14.4]	6.5 [0.2; 17.7]	8.2 [4.0; 12.3]	9.1 [6.8; 11.7]	0.02*	0.42†	0.08†	0.77†	0.43†	0.43†
CD4+ (cells/ μ L)	444 [290; 655]	358 [278; 585]	342 [246; 477]	360 [195; 538]	543 [393; 794]	<0.001*	0.21†	<0.001†	<0.001†	<0.001†	<0.001†
HIV-RNA (log ₁₀ copies/mL)	1.69 [1.69; 4.42]	3.76 [1.69; 4.62]	4.88 [1.98; 4.68]	2.27 [1.69; 4.62]	1.69 [1.69; 2.94]	<0.001*	0.37†	<0.001†	<0.001†	0.002†	0.002†
HIV-RNA <50 copies/mL	147 [51%]	36 [40%]	4 [16%]	25 [46%]	82 [71%]	<0.001†	0.03†	<0.001†	<0.001†	0.002†	0.002†
eGFR (mL/min/1.73 m ²)	102 [87; 112]	104 [89; 113]	110 [96; 115]	101 [88; 112]	98 [84; 106]	0.04*	0.11†	0.11†	0.005†	0.22†	0.22†
eGFR <60 mL/min/1.73 m ²	15 [5%]	6 [7%]	1 [4%]	3 [5%]	5 [4%]	0.88†	0.99†	0.53†	0.99†	0.71†	0.71†
eGFR between 60 and 90 mL/min/1.73 m ²	78 [27%]	24 [27%]	4 (16%)	15 [27%]	35 [30%]	0.55†	0.42†	0.64†	0.21†	0.72†	0.72†

ART = antiretroviral therapy, ATV/r = atazanavir/ritonavir, CD4 = cluster differentiation 4, DRV/r = darunavir/ritonavir, eGFR = estimated glomerular filtration rate, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IVDU = intravenous drug user, LPV/r = lopinavir/ritonavir, MSM = man who have sex with man, NNRTI = non-nucleoside reverse transcriptase inhibitor, RNA = ribonucleic acid.
 *Kruskal–Wallis test.
 †Wilcoxon rank sum test.
 ‡ χ^2 /Fisher exact test.

TABLE 3. Proportions of Patients Treated With Tenofovir Plus Emtricitabine or Lamivudine and Either Atazanavir/Ritonavir or Darunavir/Ritonavir or Lopinavir/Ritonavir or a Non-Nucleoside Reverse Transcriptase Inhibitor and With a Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) Lower or Greater Than 3%

Treatment Group	Mean Percent Change in eGFR Greater Than 3% per Year	Mean Percent Change in eGFR Lower Than 3% per Year	P Value
ATV/r	40 (8.5%)	431 (91.5%)	0.014
LPV/r	20 (6%)	313 (94%)	
DRV/r	6 (3.3%)	175 (96.7%)	
NNRTI	30 (4.5%)	643 (95.5%)	

ATV/r = atazanavir/ritonavir, DRV/r = darunavir/ritonavir, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor.

LPV/r [mean slope (95% CI): -0.07 (-0.99 ; $+0.86$) mL/min/1.73 m² per year].

Patients Treated With ABC

Among patients treated with ABC ($n = 286$), statistically significant differences in baseline characteristics between these groups were observed with regard to BMI, HIV risk factor, previous AIDS diagnosis, nadir and current CD4+ count, ART-naïve status, calendar year, years since ART initiation, HIV-RNA, proportion of subjects with undetectable viral load and eGFR (Table 2).

At the end of follow-up (i.e., stop of any drug of the regimen or lost to follow-up or data freezing [September 2014]), the number of patients in each treatment group was 280 (98% of the 286 initially included: 4 died and 2 were lost to follow-up, after a median (IQR) follow-up of 2.5 (1.2; 4.9) years. The numbers of patients at the end of the observational period in the different groups were: 90/90, 100% (no deaths or lost to follow-up), after a median (IQR) follow-up of 2.8 (1.3; 4.9) years in the ATV/r group, 55/55, 100% (no deaths or lost to follow-up), after

TABLE 4. Multivariate Mixed Linear Model: Differences Between PI/r-Based Regimens in Estimated Glomerular Filtration Rate (eGFR) Changes in Patients Treated With Tenofovir Plus Emtricitabine or Lamivudine and Either Atazanavir/Ritonavir or Darunavir/Ritonavir or Lopinavir/Ritonavir or a Non-Nucleoside Reverse Transcriptase Inhibitor

	Difference in eGFR Slope (mL/min/1.73 m ² per year) [95% CI]	P Value
ATV/r vs. DRV/r	-0.83 [-1.65 , -0.02]	0.04
ATV/r vs. LPV/r	-0.40 [-0.92 , $+0.11$]	0.12
DRV/r vs. LPV/r	$+0.43$ [-0.43 , $+1.29$]	0.33

ATV/r = atazanavir/ritonavir, DRV/r = darunavir/ritonavir, LPV/r = lopinavir/ritonavir, PI/r = protease inhibitor boosted with ritonavir.

a median (IQR) follow-up of 1.5 (1.0; 2.0) years in the LPV/r group, 25/25, 100% (no deaths or lost to follow-up), after a median (IQR) follow-up of 1.8 (0.7; 4.2) years in the DRV/r group and 110/116, 95% (4 deaths and 2 lost to follow-up), after a median (IQR) follow-up of 3.4 (1.3; 5.9) years in the NNRTI group.

After a median (IQR) follow-up of 2.5 (1.2; 4.9) years (2.8 [1.3; 4.9], 1.5 [1.0; 2.0], 1.8 [0.7; 4.2], and 3.4 [1.3; 5.9] years, in patients treated with ATV/r, DRV/r, LPV/r, and NNRTIs, respectively; $P = 0.001$ for ATV/r vs. DRV/r, $P = 0.26$ for ATV/r vs. NNRTI, $P < 0.001$ for DRV/r vs. NNRTI, $P = 0.003$ for LPV/r vs. NNRTI), a modification of any component of the regimen occurred in 177 (62%) patients (in 56 [62%], 16 [64%], 49 [89%], and 56 [48%] patients treated with ATV/r, DRV/r, LPV/r and NNRTIs, respectively; $P < 0.001$ for the comparison LPV/r vs. NNRTI; no significant differences for other comparisons between regimens). Among patients with modifications in the regimen, eGFR at the time of modification was 99 (84; 111) (99 [86; 112], 105 [97; 114], 97 [90; 106], and 99 [83; 111] mL/min/1.73 m² in patients treated with ATV/r, DRV/r, LPV/r and NNRTI, respectively; no significant differences for all comparisons between regimens).

The number of eGFR determinations per patient during follow-up was 8 (3; 16) (8 [4; 17], 4 [3; 7], 7 [3; 16], and 11 [3; 17] in patients treated with ATV/r, DRV/r, LPV/r, and NNRTI, respectively; $P = 0.002$ for the comparisons ATV/r vs. DRV/r and DRV/r vs. NNRTI, no significant differences for other comparisons between regimens).

Crude eGFR slopes (95% CI) were $+0.41$ (-0.25 ; $+1.06$), $+1.45$ (-1.07 ; $+3.97$), -0.14 (-1.06 ; $+0.79$), and $+0.004$ (-0.53 ; $+0.54$) mL/min/1.73 m² per year for ATV/r, DRV/r, LPV/r, and NNRTI, respectively. Based on 2406 eGFR determinations, adjusted eGFR slopes (95% CI) were $+0.54$ (-0.08 ; $+1.16$), $+2.09$ (-0.03 ; $+4.21$), $+0.07$ (-0.77 ; $+0.91$), and $+0.33$ (-0.17 ; $+0.82$) mL/min/1.73 m² per year for ATV/r, DRV/r, LPV/r, and NNRTI, respectively, with no significant differences among groups (ATV/r vs. DRV/r: $P = 0.16$; ATV/r vs. LPV/r: $P = 0.36$; DRV/r vs. LPV/r: $P = 0.08$).

Among the 286 patients included in this study, 11 (4%) had a decline in eGFR $\leq 3\%$ per year without significant differences among treatment groups ($P = 0.150$) (Table 6).

Among subjects with a baseline eGFR ≥ 90 mL/min/1.73 m², 3 of 208 (1.4%) patients treated with NNRTI developed CKD (crude incidence rate [95% CI]: 9.87 [1.86; 24.2] per 1000-PYFU) and none in patients treated with PIs/r.

Results of the multivariate mixed linear model are shown in Tables 7 and 8.

DISCUSSION

Known factors associated with an increased risk of CKD in HIV-infected individuals include older age, female sex, diabetes, hypertension, injection drug use, coinfection with HCV, lower CD4+ cell count, specific antiretroviral drugs (including TDF, particularly when associated with a PI/r, such as ATV/r, LPV/r or indinavir), history of acute kidney injury, higher HIV-RNA level.^{13,35,36} To the best of our knowledge, our study is the first investigating eGFR trajectories with different antiretrovirals and, specifically, with DRV/r; thus a direct comparison between our results and those from previous studies having the development of CKD as end-point is difficult. Nonetheless, our findings seem consistent with those of the studies mentioned above: we found that, in patients treated with TDF, a more rapid eGFR decline was independently associated with the use of

TABLE 5. Multivariate Mixed Linear Model (Including 1635 Patients With 15,229 eGFR Determinations): Estimated Glomerular Filtration Rate (eGFR) Changes in Patients Treated With Tenofovir Plus Emtricitabine or Lamivudine and Either Atazanavir/Ritonavir or Darunavir/Ritonavir or Lopinavir/Ritonavir or a Non-Nucleoside Reverse Transcriptase Inhibitor

	eGFR Slope (mL/min/1.73 m ² per Year) [95% CI]	P Value
Decline (per year longer of follow-up)	-0.20 [-0.42; +0.02]	0.07
PI/r or NNRTI component of the regimen		<0.001
ATV/r	-1.06 [-1.44; -0.69]	<0.001
DRV/r	-0.23 [-1.02; +0.55]	0.56
LPV/r	-0.66 [-1.13; -0.20]	0.005
NNRTI	Ref	
Baseline calendar year (per year higher)	+0.24 [+0.06; +0.42]	0.01
Hypertension		<0.001
Yes	-2.32 [-3.37; -1.28]	
No	Ref	
CD4+ nadir (per 100-cells/ μ L higher)	+0.29 [+0.08; +0.51]	0.007
Baseline eGFR (per mL/min/1.73 m ² higher)	-0.21 [-0.24; -0.19]	<0.001
Current CD4+ (per 100-cells/ μ L higher)	-0.26 [-0.35; -0.17]	<0.001
HCV infection		0.82
Yes	-0.03 [-1.28; +1.23]	0.96
Unknown	+0.21 [-0.52; +0.95]	0.56
No	Ref	
ART-naive status		0.12
Yes	-0.85 [-1.93; +0.24]	
No	Ref	
Type-2 diabetes		0.99
Yes	+0.01 [-1.61; +1.63]	
No	Ref	
Years of ART (per 10-years longer)	+0.38 [-0.72; +1.48]	0.49
Years since HIV diagnosis (per 10-years higher)	-0.64 [-1.37; +0.09]	0.08
Current HIV-RNA		
≥ 50 copies/mL	+0.25 [-0.14; +0.63]	0.21
<50 copies/mL	Ref	

95% CI = 95% confidence interval, ART = antiretroviral therapy, ATV/r = atazanavir/ritonavir, CD4 = cluster differentiation 4, DRV/r = darunavir/ritonavir, HCV = hepatitis C virus, HIV = human immunodeficiency virus, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI/r = protease inhibitor boosted with ritonavir, Ref = reference class, RNA = ribonucleic acid.

Current CD4+ and current HIV-RNA were used as time-updated variables.

ATV/r and of LPV/r and also with hypertension, lower nadir CD4+ cell counts, and higher baseline eGFR. However, we also observed an independent association between eGFR decline and current CD4+ cell counts and baseline calendar years. In the D:A:D cohort, advanced CKD/end-stage renal disease (ESRD)

TABLE 6. Proportions of Patients Treated With Abacavir Plus Lamivudine and Either Atazanavir/Ritonavir or Darunavir/Ritonavir or Lopinavir/Ritonavir or a Non-Nucleoside Reverse Transcriptase Inhibitor and With a Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) Lower or Greater Than 3%

Treatment Group	Mean Percent Change in eGFR Greater Than 3% per Year	Mean Percent Change in eGFR Lower Than 3% per Year	P Value
ATV/r	1 (1%)	89 (99%)	0.15
LPV/r	2 (4%)	53 (96%)	
DRV/r	0	25 (100%)	
NNRTI	8 (7%)	112 (93%)	

ATV/r = atazanavir/ritonavir, DRV/r = darunavir/ritonavir, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor.

was independently associated with lower current CD4+ cell count (1.37 [95% CI, 1.19–1.56]/halving).³⁷ Similarly, in the NA-ACCORD cohort, in which black race accounts for roughly one-third of enrolled patients, higher baseline CD4+ counts were independently associated with a lower incident rate ratio of ESRD.³⁸ In both these studies, however, one-third of patients not receiving ART and eGFR slopes were not evaluated: the apparent inconsistency between these previous and our finding may thus be due to differences in study designs, end-points, and study populations. Finally, it must be underlined that, in our study, patients treated with DRV/r had a more recent baseline and lower baseline CD4+ counts: thus, the effect of current CD4+ counts and calendar year on eGFR slopes may be, at least in part, driven by the PI/r received.

Ryom et al³⁷ found no consistent or significant associations between current or previous use of any antiretroviral and advanced CKD/ESRD. However, this lack of association has not been confirmed in a subsequent analysis of data collected by the same cohort²³ and, using data from multiple cohorts, the same authors were able to confirm the association between use

TABLE 7. Multivariate Mixed Linear Model: Differences Between PI/r-Based Regimens in Estimated Glomerular Filtration Rate (eGFR) Changes in Patients Treated With Abacavir Plus Lamivudine and Either Atazanavir/Ritonavir or Darunavir/Ritonavir or Lopinavir/Ritonavir or a Non-Nucleoside Reverse Transcriptase Inhibitor

	Difference in eGFR Slope (mL/min/1.73 m ² per year) [95% CI]	P Value
ATV/r vs. DRV/r	-1.55 [-3.74, +0.63]	0.16
ATV/r vs. LPV/r	+0.47 [-0.56, +1.51]	0.36
DRV/r vs. LPV/r	+2.03 [-0.23, +4.28]	0.08

ATV/r = atazanavir/ritonavir, DRV/r = darunavir/ritonavir, LPV/r = lopinavir/ritonavir, PI/r = protease inhibitor boosted with ritonavir.

TABLE 8. Multivariate Mixed Linear Model: Estimated Glomerular Filtration Rate (eGFR) Changes in Patients Treated With Abacavir Plus Lamivudine and Either Atazanavir/Ritonavir or Darunavir/Ritonavir or Lopinavir/Ritonavir or a Non-Nucleoside Reverse Transcriptase Inhibitor

	eGFR Slope (mL/min/1.73 m ² per Year) [95% CI]	P Value
Decline (per year longer of follow-up)	+0.33 [−0.17; +0.82]	0.19
PI/r or NNRTI component of the regimen		0.33
ATV/r	+0.22 [−0.56; +1.00]	0.58
DRV/r	+1.77 [−0.39; +3.93]	0.11
LPV/r	−0.26 [−1.23; +0.71]	0.6
NNRTI	Ref	
Baseline calendar year (per year higher)	−0.24 [−0.67; +0.20]	0.28
Hypertension		0.001
Yes	−4.72 [−7.57; −1.87]	
No	Ref	
Nadir CD4+ (per 100-cells/μL higher)	+0.76 [+0.22; +0.13]	0.006
Baseline eGFR (per mL/min/1.73 m ² higher)	−0.26 [−0.31; −0.20]	<0.001
Current CD4+ (per 100-cells/μL higher)	−0.34 [−0.55; −0.13]	0.002
HCV infection		0.06
Yes	+2.58 [−1.39; +6.54]	0.2
Unknown	−1.82 [−4.07; +0.43]	0.11
No	Ref	
ART-naïve status		0.85
Yes	−0.32 [−3.70; +3.06]	
No	Ref	
Type 2 diabetes		0.05
Yes	+4.21 [−0.14; +8.56]	
No	Ref	
Years of ART (per 10-years longer)	−1.24 [−4.42; +1.95]	0.44
Years since first HIV diagnosis (per 10-years higher)	+1.79 [−0.47; +4.05]	0.12
Current HIV-RNA		
≥50 copies/mL	+0.73 [−1.85; +0.40]	0.2
<50 copies/mL	Ref	

95% CI = 95% confidence interval, ART = antiretroviral therapy, ATV/r = atazanavir/ritonavir, CD4 = cluster differentiation 4, DRV/r = darunavir/ritonavir, HCV = hepatitis C virus, HIV = human immunodeficiency virus, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI/r = protease inhibitor boosted with ritonavir, Ref = reference class, RNA = ribonucleic acid.

Current CD4+ and current HIV-RNA were used as time-updated variables.

of certain antiretroviral drugs and the development of CKD.³⁶ Our result may help in explaining how a cumulative exposure to ATV/r and LPV/r leads to an increased and cumulative risk of CKD.²³

Not surprisingly, and on par with other cohort studies that found an independent association between pre-existing renal impairment and CKD,^{37,39–42} we observed a more rapid decline of eGFR in patients with lower baseline eGFR.

Changes in eGFR and creatinine clearance in patients treated with a PI/r may be in part due to the known inhibitory effect of RTV on tubular creatinine secretion via multidrug and toxin extrusion 1 (MATE1) complex.^{43,44} Data from in vitro experiments suggest that RTV has minimal effect on multidrug resistance protein 4 (MRP4), the apical tubular tenofovir (TFV) transporter.⁴⁵ However, increased tubular TFV exposure may result from the inhibitory effect of RTV on the P-glycoprotein (P-gp).⁴⁶ In patients treated with LPV/r, plasma exposure to TFV was increased by 50% and the intracellular TFV-diphosphate (DP) AUC(0–4) was increased by 59%, with respect to those receiving nevirapine;⁴⁷ it has been hypothesized that this finding is the consequence of an increased absorption

of TDF.⁴⁸ LPV/r has been also shown to reduce TFV renal clearance by 17.5%,⁴⁹ but this might simply reflect the effect of RTV rather than that of LPV.⁴⁴ It remains unclear whether LPV/r has intrinsic nephrotoxic properties or whether LPV/r merely enhances the nephrotoxicity of TDF,⁴⁴ but it should be noted that in the D:A:D cohort the use of LPV/r was associated with a greater risk of CKD independent of the use of TDF^{19,23} and that HIV-infected women taking TDF and LPV/r had significantly more renal events compared with those treated with TDF and NVP.⁴²

When TFV-DP concentrations within peripheral blood mononuclear cells were compared among individuals receiving either ATV/r or DRV/r-based regimens, there was a trend toward higher TFV-DP concentrations among women and participants receiving ATV/r.⁵⁰ ATV/r has been associated with increased risks of reduced GFR, nephrolithiasis, proximal tubular dysfunction, interstitial nephritis, and acute kidney injury, independent of concurrent TDF use.^{13,19,20,31,36,51–54} Renal function changes significantly improved (or declined less) with EFV-including regimens compared with ATV/r-including regimens in the A5202 Study (in which treatment-naïve patients

were randomized to ABC/3TC or TDF/FTC with open-label ATV/r or EFV), independent of the backbone.⁵⁵ Thus, the association of ATV/r and TDF may be particularly at risk for kidney because of cumulative or synergistic toxicity, which may explain the faster decline in eGFR that we observed in patients treated with these 2 drugs. The characteristics of our study do not allow us to speculate further on this issue. However, it seems unlikely that the greater decrease in eGFR that we observed in patients receiving ATV/r was merely due to an enhanced TDF toxicity, linked to an increase in TFV concentrations in tubular cells due to the coadministration of RTV: if this would be true, we should have observed similar eGFR slopes in patients treated with DRV/r. It seems unlikely as well that the greater decrease in eGFR that we observed in patients receiving ATV/r was due solely to the inhibition of the tubular secretion of creatinine caused by RTV;⁴³ again, if this was the only explanation we should have observed a similar eGFR decrease in patients treated with DRV/r (and even more with LPV/r, due to the 2-fold RTV dose prescribed). Furthermore, it has been observed that eGFR improved less in patients randomized to first-line ATV/r + TDF/FTC than in those randomized to other regimens when it was estimated by cystatin C-based equations, suggesting that ATV/r likely has an effect on eGFR independent of any possible serum creatinine increase due simply to MATE1 inhibition.⁵⁵

An enhanced TDF toxicity might in part explain differences in eGFR slopes between patients who received LPV/r and those treated with DRV/r, because the dose of RTV for the former is 2-fold compared with the latter.

Darunavir was not included (or not specifically mentioned^{23,36}) in previous large analyses on the relationship between antiretroviral use and changes in eGFR or the development of CKD.^{18,20} To our knowledge, our study is the first investigating specifically the impact of DRV/r on the kidney and suggests that, like NNRTIs (and differently from other PIs), DRV/r has minimal (if any) impact on kidney function.

A new prodrug of tenofovir (tenofovir alafenamide—TAF), which yields lower plasma concentrations of TFV, will be soon available.⁵⁶ Patients treated with elvitegravir/cobicistat/FTC/TAF had fewer renal adverse event-related discontinuations (none with TAF regimen), significantly smaller decreases in eGFR, and significantly less proteinuria and tubulopathy than those treated with elvitegravir/cobicistat/FTC/TDF.⁵⁷ This suggests that TAF has less renal toxicity compared with TDF; however, we cannot anticipate if the differences that we observed between studied PIs/r would persist when TDF will be substituted with TAF.

Contrary to what we found in patients treated with TDF, in those receiving ABC we did not observe differences in eGFR slopes between PIs/r. This might mean that different impacts of PIs/r on eGFR are evident only when TDF is coadministered, because of a synergistic renal toxicity; however, we cannot exclude that we did not have sufficient statistical power to elicit differences between PIs/r in this group of patients. Indeed, among treatment-naïve patients randomized to start their first-line regimen with ATV/r plus TDF and FTC or ATV/r plus ABC and 3TC, those starting TDF showed a reduction in eGFR both at weeks 48 and 96, while those starting ABC showed an increase in eGFR both at weeks 48 and 96.³³ In a substudy, no difference was observed between ATV/r and EFV in patients randomized to ABC/3TC.⁵⁵ Altogether, these findings suggest that the more rapid decline in eGFR observed in patients treated with ATV/r and TDF is due to an enhanced toxicity of TDF by ATV/r (and possibly to a “synergistic”

toxicity of these 2 drugs) rather than a predominant kidney toxicity of ATV/r.

The main limitation of our study is its retrospective design. Although we tried to correct for all measurable confounders, we cannot exclude that some unknown or unmeasured confounding still remained. A further limit is the relatively small sample size of the group treated with ABC-based regimens. However, as ABC is currently recommended by most recent guidelines only in combination with dolutegravir,^{2,4} for patients treated with a PI/r the main clinical concern is the association with TDF.

We were unable to assess the influence of some potential and relatively common causes of progressive impaired renal function, such as renal artery stenosis, nephrolithiasis, lupus erythematosus, abuse of non-steroidal anti-inflammatory drugs, as such conditions were not systematically investigated. Furthermore, not all patients had regular proteinuria measurement: thus, we were not able to assess whether there are different risks of tubulopathy with different PI/r.

To conclude, among patients receiving TDF (and FTC or 3TC), declines in eGFR trajectories were small for all regimens, but smaller in those receiving DRV/r or NNRTIs than in those treated with ATV/r or LPV/r. eGFR trajectories in patients treated with DRV/r plus TDF and FTC or 3TC were not statistically different from those observed in patients receiving a NNRTI plus TDF and FTC or 3TC. In patients receiving ABC/3TC, no between regimen differences were observed.

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