

Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir

Jim Young^a, Juliane Schäfer^a, Christoph A. Fux^b, Hansjakob Furrer^b,
Enos Bernasconi^c, Pietro Vernazza^d, Alexandra Calmy^e,
Matthias Cavassini^f, Rainer Weber^g, Manuel Battegay^h,
Heiner C. Bucher^{a,h}, the Swiss HIV Cohort Study

Background: Tenofovir is associated with reduced renal function, but it is not clear whether there is a greater decline in renal function when tenofovir is co-administered with a boosted protease inhibitor rather than with a nonnucleoside reverse transcriptase inhibitor (NNRTI).

Methods: We calculated the estimated glomerular filtration rate (eGFR) for patients in the Swiss HIV Cohort Study. We estimated the difference in eGFR over time between first therapies containing tenofovir and either the NNRTI efavirenz or the protease inhibitors lopinavir (LPV/r) or atazanavir (ATV/r), both boosted with ritonavir.

Results: Patients on a first therapy of tenofovir co-administered with efavirenz ($n = 484$), LPV/r ($n = 269$) and ATV/r ($n = 187$) were followed for a median of 1.7, 1.2 and 1.3 years, respectively. Relative to tenofovir and efavirenz, the estimated difference in eGFR for tenofovir and LPV/r was -2.6 ml/min per 1.73 m² [95% confidence interval (CI) -7.3 to 2.2] during the first 6 months of therapy, then followed by a difference of 0.0 ml/min per 1.73 m² (95% CI -1.1 to 1.1) for each additional 6 months of therapy. Relative to tenofovir and efavirenz, the estimated difference in eGFR for tenofovir and ATV/r was -7.6 ml/min per 1.73 m² (95% CI -11.8 to -3.4) during the first 6 months of therapy, then followed by a difference of -0.5 ml/min per 1.73 m² (95% CI -1.6 to 0.7) for each additional 6 months of therapy.

Conclusion: Tenofovir with either boosted protease inhibitor leads to a greater initial decline in eGFR than tenofovir with efavirenz; this decline may be worse with ATV/r than with LPV/r.

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Introduction

Tenofovir disoproxil fumarate (tenofovir) is now a preferred nucleoside or nucleotide reverse transcriptase

inhibitor (NRTI) when starting therapy for all patients with HIV except pregnant women [1]. Tenofovir is mainly eliminated by the kidneys and its use is associated with reduced renal function [2]. Regular monitoring of

^aBasel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, ^bDivision of Infectious Diseases, University Hospital Bern and University of Bern, Bern, ^cRegional Hospital of Lugano, Lugano, ^dDivision of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St Gallen, St Gallen, ^eDivision of Infectious Diseases, University Hospital Geneva, Geneva, ^fDivision of Infectious Diseases, University Hospital Lausanne, Lausanne, ^gDivision of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, and ^hDivision of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland.

Correspondence to Jim Young, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, CH-4031 Basel, Switzerland.

Tel: +41 61 265 3100; fax: +41 61 265 3109; e-mail: jyoung@uhbs.ch

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renal function is, therefore, recommended for all patients on tenofovir [1].

Recommended first therapy for patients with HIV is a combination of two NRTIs together with a ritonavir-boosted protease inhibitor or with efavirenz, a non-NRTI (NNRTI) [1]. Evidence from randomized controlled trials and observational studies is mixed on whether there is a greater decline in renal function when tenofovir is co-administered with a boosted protease inhibitor rather than with a NNRTI [3–11]. The use of different formulas to calculate the estimated glomerular filtration rate (eGFR) as a measure of renal function, the use of different measurement frequencies and techniques, different study designs and different statistical methods, all add to the variability of results, making it difficult to interpret the effect of the various antiretroviral drugs on renal function [10].

In this study, we used observational data from the Swiss HIV Cohort Study (SHCS) to compare eGFR over time in patients with HIV starting a first therapy with tenofovir and either efavirenz or ritonavir-boosted lopinavir (LPV/r) or ritonavir-boosted atazanavir (ATV/r), the two most commonly used protease inhibitors in the SHCS. We modelled eGFR in these observational data using statistical methods that both adjust for informative censoring and allow for repeated measurements over time.

Methods

Patients

The SHCS is a multicentre, prospective, observational cohort study with continuing enrolment of HIV-infected adults and routine follow-up scheduled every 6 months [12]. Our population of interest was all therapy-naïve patients starting first therapy with tenofovir and either efavirenz, LPV/r or ATV/r (and usually one other NRTI) after 1 January 2002, when serum creatinine measurements were included in the SHCS database. Our sample included all patients from this population with at least one calibrated serum creatinine measurement after starting therapy and both a viral load (HIV-RNA) and CD4⁺ T-cell count measurement less than 6 months before starting therapy. Creatinine measurements from SHCS centre laboratories were calibrated because different SHCS centres use different creatinine measurement techniques. However, in a sensitivity analysis we also included uncalibrated measurements from SHCS patients seen by private physicians. As a measure of renal function, we calculated the eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [13], but in sensitivity analyses we also report results for the Modification of Diet in Renal Disease (MDRD) Study equation [14] and for the Cockcroft–Gault equation [15]. We followed patients from the start of therapy until their

last recorded measurement to date (administrative censoring) or censored patients when they dropped out of the SHCS or stopped taking any one of the four drugs: tenofovir, efavirenz, LPV/r or ATV/r.

Statistical analyses

We used marginal structural models for repeated measures to estimate the difference over time in eGFR between two therapies [16,17]. We took efavirenz as the common comparator for therapy with either LPV/r or ATV/r, and modelled eGFR over time for patients on efavirenz as a time-dependent intercept (a restricted cubic spline with five knots at the 5th, 27.5th, 50th, 72.5th and 95th percentiles for the months since starting therapy [18]). We modelled the difference in eGFR for patients on LPV/r or ATV/r using a piecewise linear spline with a change in slope after 6 months of therapy. Our choice of spline was based on an earlier study in which an initial decline in eGFR during the first 6 months of therapy was followed by little change between 6 and 24 months [9]. We fitted the above model for eGFR over time using generalized estimating equations (GEEs) with an independent working covariance matrix and with inverse probability weights to adjust for differences both in the characteristics of patients starting each therapy and in the characteristics of patients remaining on each therapy over time [19]. To make these adjustments, we constructed two sets of inverse probability weights – point of treatment weights and censoring weights [17,20] – using variables that may determine either the choice of the initial therapy, dropout from the SHCS or the decision to change therapy. In weighted analyses, each observation was weighted by the product of these two sets of weights. To construct each set of weights, we used logistic regression models with covariates such as sex, ethnicity, intravenous drug use as the likely mode of HIV-transmission, duration of HIV-infection, age, advanced HIV infection, diabetes, hypertension, chronic hepatitis B or hepatitis C infection, viral load and CD4⁺ T-cell count (see Appendix, Supplemental Digital Content 1, <http://links.lww.com/QAD/A197>). We also give results for an unadjusted analysis – a standard repeated measures model fit using GEE without weights [21].

We report results for three sensitivity analyses. First, we removed unusually low values of eGFR (<30 ml/min per 1.73 m²) to see whether our estimates were robust to outliers. Second, we included both calibrated and uncalibrated serum creatinine measurements in our analyses. Third, we used both the MDRD Study equation and the Cockcroft–Gault equation as alternative measures of eGFR.

For each analysis, we report an estimate [and 95% confidence interval (CI)] of the difference between a protease inhibitor-based therapy and the efavirenz-based reference therapy. We used SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) for our analyses; and for

graphics, we used R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria) and the R add-on package ggplot2 version 0.8.9 [22].

Results

Patient characteristics

As of March 2011, 1720 patients in the SHCS started a first therapy after 1 January 2002 with both tenofovir and either efavirenz, LPV/r or ATV/r. Of these, 1 053 (61%) patients had at least one calibrated serum creatinine measurement after starting therapy, and 940 (55%) also had measurements of viral load and CD4⁺ T-cell count less than 6 months before starting therapy (Table 1). Compared with patients starting tenofovir and efavirenz, those starting tenofovir and LPV/r were more likely to start with an advanced stage of infection and with a lower CD4⁺ T-cell count, whereas those starting tenofovir and either protease inhibitor were more likely to have been

infected with HIV through drug use and chronically co-infected with hepatitis B or hepatitis C (Table 2).

Renal function prior to therapy

Of the 940 patients in our sample, only 671 (71%) had a calibrated creatinine measurement within 6 months before starting therapy (Table 1). Among these patients, the median eGFR before starting therapy was 105, 108 and 109 for those starting tenofovir with efavirenz, LPV/r and ATV/r, respectively, whereas the median eGFR after starting therapy was 105, 102 and 99, respectively. The median time between before and after measurements was 5 months (3 months for patients starting tenofovir with ATV/r).

Renal function over time

Patients starting tenofovir with efavirenz, LPV/r and ATV/r were followed for a median of 1.7 [interquartile range (IQR) 0.7–3.6], 1.2 (IQR 0.6–2.3) and 1.3 (IQR 0.6–2.6) years, respectively. During this time, patients starting tenofovir with efavirenz, LPV/r and ATV/r had a

Table 1. Patient flow for those starting first therapy with co-administered tenofovir.

	Efavirenz	LPV/r	ATV/r
Number of patients starting after 1 January 2002	909	451	360
Patients with ≥ 1 calibrated or uncalibrated creatinine measurement after starting therapy (%)	84	83	88
Along with HIV RNA and CD4 ⁺ T-cell count within 6 months before starting therapy (%) (sensitivity analysis)	78	68	80
Patients with ≥ 1 calibrated creatinine measurement after starting therapy (%)	57	73	58
Along with HIV RNA and CD4 ⁺ T-cell count within 6 months before starting therapy (%) (main analysis)	53	60	52
Number of patients in the main analysis	484	269	187
With a calibrated creatinine measurement within 6 months before starting therapy (%)	70	67	80
Last eGFR ^a before starting therapy (ml/min per 1.73 m ²)			
Median (IQR)	105 (92–116)	108 (98–117)	109 (92–118)
First eGFR ^a after starting therapy (ml/min per 1.73 m ²)			
Median, (IQR)	105 (94–114)	102 (88–112)	99 (85–112)
Time between these two eGFR ^a (months)			
Median (IQR)	5 (3–6)	5 (2–7)	3 (2–6)
Followed until ^b			
Administrative censoring (%)	61	31	54
Patient dropped out of SHCS (%)	2	2	1
Patient stopped taking tenofovir (%)	21	26	28
Patient stopped taking efavirenz, LPV/r or ATV/r (%)	33	56	40
Time to administrative censoring (months)			
Median (IQR)	28 (11–50)	28 (14–46)	20 (8–39)
Time to patient dropped out of SHCS (months)			
Median (IQR)	10 (6–48)	14 (1–26)	7 (7–7)
Time to patient stopped taking tenofovir (months)			
Median (IQR)	12 (6–26)	12 (4–22)	11 (6–21)
Time to patient stopped taking efavirenz, LPV/r or ATV/r (months)			
Median (IQR)	12 (5–24)	9 (5–15)	11 (5–21)

The number of patients starting a first therapy with tenofovir and either efavirenz, ritonavir-boosted lopinavir (LPV/r) or ritonavir-boosted atazanavir (ATV/r) and for patients in the main analysis, their estimated glomerular filtration rate (eGFR^a) before and after starting therapy, if known, and length of follow-up. IQR, interquartile range; SHCS, Swiss HIV Cohort Study.

^aEstimated glomerular filtration rate (ml/min per 1.73m²) calculated with the Chronic Kidney Disease Collaboration (CKD-EPI) equation [13].

^bMany patients stopped taking both tenofovir and efavirenz, LPV/r or ATV/r (17, 15 and 23% of the patients starting efavirenz, LPV/r and ATV/r, respectively).

Table 2. Characteristics of patients starting a first therapy.

Characteristic	Measure or category	Main component of therapy		
		Efavirenz ^a (n = 484)	LPV/r (n = 269)	ATV/r (n = 187)
HIV RNA (log ₁₀ copies/ml)	Median (IQR)	4.7 (4.3–5.2)	5.0 (4.4–5.5)	4.8 (4.3–5.2)
CD4 ⁺ T-cell count (cells/μl)	Median (IQR)	242 (158–320)	203 (81–296)	240 (168–308)
Age (years)	Median (IQR)	40 (34–47)	39 (33–46)	38 (32–46)
Sex (%)	Female	17	26	23
Ethnicity (%)	Black	16	14	12
Likely mode of HIV transmission (%)	Intravenous drug use	6	12	18
Advanced stage of infection (%)	CDC group C	14	27	11
Diabetes mellitus ^b (%)	Yes	3	1	3
Chronic hepatitis B or hepatitis C (%)	Yes	14	22	28
Hypertension ^c (%)	Yes	19	19	22
Duration of HIV-infection ^d (years)	Median (IQR)	1.4 (0.2–3.8)	0.4 (0.1–3.6)	2.0 (0.3–5.2)
Other antiretroviral drugs (%)	Emtricitabine	76	81	87
	Lamivudine	21	11	9
	None	1	0	2
	Others	2	7	2

Therapy with tenofovir and either efavirenz, ritonavir-boosted lopinavir (LPV/r) or ritonavir-boosted atazanavir (ATV/r). CDC, Center for Disease Control and Prevention; IQR, interquartile range.

^aOne patient on efavirenz, tenofovir and ATV/r is included in the comparison with LPV/r, but not in the comparison with ATV/r; one patient on efavirenz, tenofovir and LPV/r is included in the comparison with ATV/r, but not in the comparison with LPV/r.

^bClinical diagnosis of diabetes mellitus, plasma glucose > 11.1 mmol/l or taking antidiabetic agents or insulin prior to starting first therapy.

^cSBP ≥ 140 mmHg, DBP ≥ 90 mmHg (≥ 135/85 mmHg in diabetic patients) or taking antihypertensive drugs prior to starting first therapy.

^dOn the basis of the date of (for patients starting efavirenz, LPV/r and ATV/r, respectively) a first documented positive test (87, 86 and 87%); a first reported positive test (9, 9 and 6%); or the cohort registration visit (4, 5 and 7%).

median of four (IQR 2–9), three (IQR 2–7) and five (IQR 2–10) calibrated serum creatinine measurements, respectively.

Mean eGFR declined over time for patients on all three tenofovir-containing therapies (Fig. 1). After starting therapy, patients on tenofovir and efavirenz had a higher eGFR on average than those on tenofovir and LPV/r (Fig. 1, top row); patients on tenofovir and ATV/r had the lowest eGFR on average (Fig. 1, bottom row).

This ranking is also seen in the estimated differences in eGFR among therapies (Table 3). Relative to tenofovir and efavirenz, the estimated adjusted difference in eGFR during the first 6 months of therapy was –2.6 (95% CI –7.3 to 2.2) for patients on tenofovir and LPV/r, and –7.6 ml/min per 1.73 m² (95% CI –11.8 to –3.4) for patients on tenofovir and ATV/r. For both protease inhibitor protease inhibitors, the initial decline in eGFR relative to efavirenz was followed by little difference between the therapies after 6 months. Comparing unadjusted and weighted models shows that adjustment via inverse probability weights reduced the apparent difference between therapies during the first 6 months for patients on LPV/r, but had little effect on this difference for patients on ATV/r.

Many of the patients in our sample were followed until they stopped taking one of the four drugs of interest (Table 1: 37, 67 and 45% of those starting tenofovir with efavirenz, LPV/r and ATV/r, respectively); often patients stopped taking two of the four drugs of interest (17, 15 and 23% of those starting tenofovir with efavirenz, LPV/r and ATV/r, respectively). Among 226 patients who

stopped taking tenofovir, the median eGFR prior to stopping was 101 ml/min per 1.73 m² (IQR 80–115), 108 (48%) of these patients have been followed for at least another year with a median eGFR after this time of 99 ml/min per 1.73 m² (IQR 81–114).

Sensitivity analyses

Estimated differences between therapies appear robust to outliers. After excluding values of eGFR below 30 ml/min per 1.73 m², the estimated difference in eGFR during the first 6 months of therapy was –2.9 ml/min per 1.73 m² (95% CI –7.7 to 1.9) for patients on tenofovir and LPV/r (three values excluded), and –7.6 ml/min per 1.73 m² (95% CI –11.9 to –3.4) for patients on tenofovir and ATV/r (two values excluded). The patients with excluded values are described in the Appendix (Supplemental Digital Content 1, <http://links.lww.com/QAD/A197>).

Of the 1 720 patients starting one of these three therapies after 1 January 2002, 1 458 (85%) patients had at least one calibrated or uncalibrated serum creatinine measurement after starting therapy, and 1 307 (76%) also had measurements of viral load and CD4⁺ T-cell count less than 6 months before starting therapy (Table 1). Compared with the main analysis, results based on both calibrated and uncalibrated serum creatinine measurements have slightly larger differences in eGFR between therapies during the first 6 months and slightly narrower CIs (Table A1, Supplemental Digital Content 1, <http://links.lww.com/QAD/A197>).

Other measures of the GFR led to a similar pattern of differences between therapies, with differences apparent

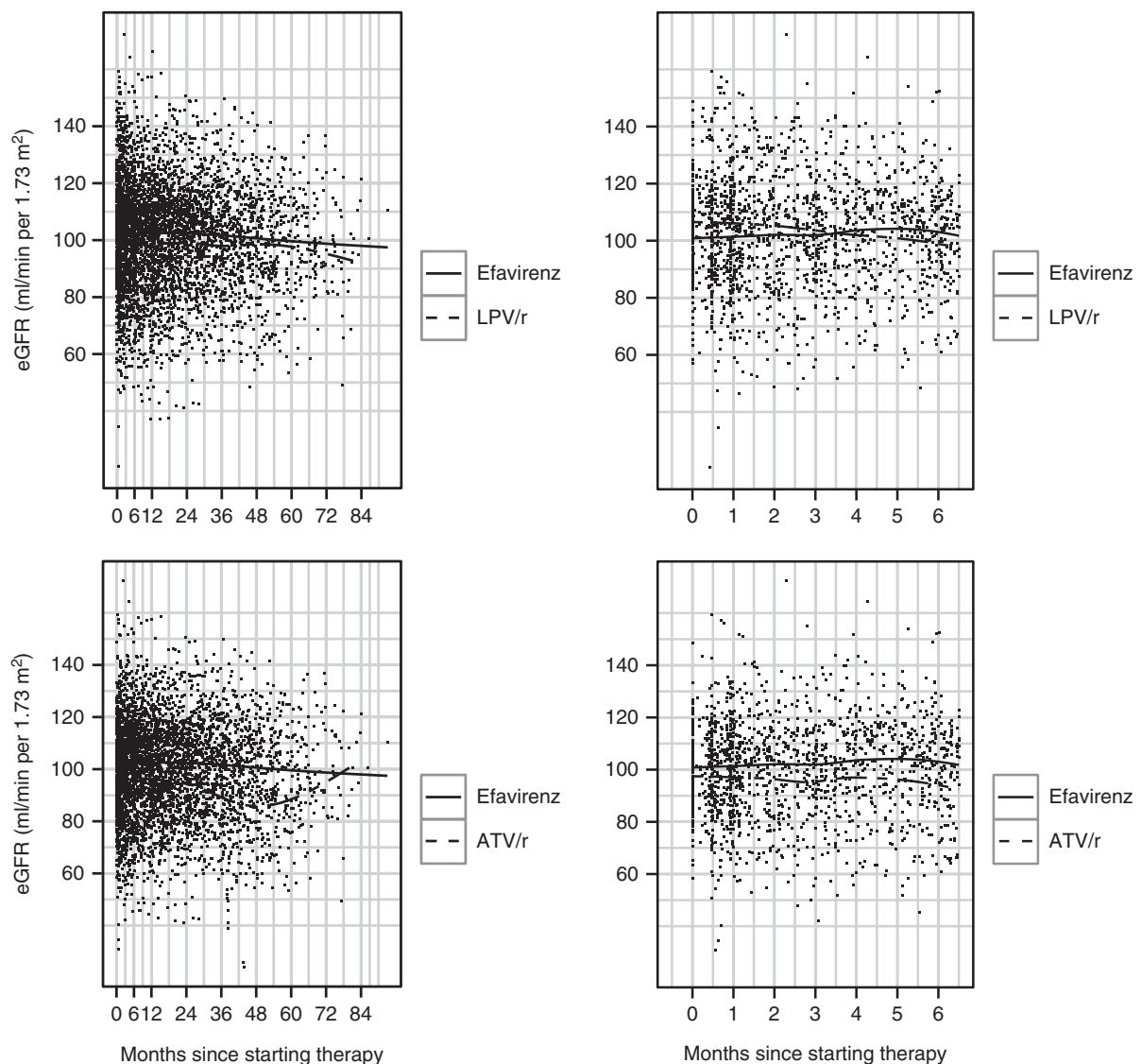


Fig. 1. Estimated glomerular filtration rate (eGFR) over time for patients starting a first therapy. Therapy with tenofovir and ritonavir-boosted lopinavir (LPV/r, top row) or tenofovir and ritonavir-boosted atazanavir (ATV/r, bottom row), both relative to patients starting therapy with tenofovir and efavirenz (both rows). The smooth curves are local averages found using the default loess smoother in the R add-on package ggplot2 [22]. Plots on the left show curves fit to all measurements; plots on the right show curves fit to just the measurements made during the first 6 months of therapy to better illustrate early changes in eGFR.

only during the first 6 months of therapy and during this period, greater differences with tenofovir and ATV/r than with tenofovir and LPV/r (Table A2, Supplemental Digital Content 1, <http://links.lww.com/QAD/A197>).

We carried out an additional sensitivity analysis suggested by a reviewer. When constructing inverse probability weights, we replaced intravenous drug use as the likely mode of HIV-transmission with current intravenous drug use. Estimated differences in eGFR were then intermediate between the unadjusted and the weighted model estimates shown in Table 3 for LPV/r-based therapy, and

were no different from the weighted model estimates shown in Table 3 for ATV/r-based therapy (Appendix, Supplemental Digital Content 1, <http://links.lww.com/QAD/A197>).

Discussion

Our results suggest that first therapies that combine tenofovir with boosted protease inhibitors, such as LPV/r or ATV/r, lead to an initial decrease in eGFR in the first 6 months of therapy relative to first therapies that

Table 3. Difference in average estimated glomerular filtration rate.

Difference in eGFR ^a per 6 months (95% CI) relative to tenofovir and efavirenz (<i>n</i> = 484)	Tenofovir and LPV/r (<i>n</i> = 269)	Tenofovir and ATV/r (<i>n</i> = 187)
Unadjusted model (months)		
≤6	-4.6 (-8.6 to -0.5)	-7.2 (-11.3 to -3.2)
>6	0.3 (-0.4 to 1.1)	-0.4 (-1.6 to 0.8)
Weighted model (months)		
≤6	-2.6 (-7.3 to 2.2)	-7.6 (-11.8 to -3.4)
>6	-0.0 (-1.1 to 1.1)	-0.5 (-1.6 to 0.7)

Differences in eGFR^a in patients starting therapy with tenofovir and ritonavir-boosted lopinavir (LPV/r) or tenofovir and ritonavir-boosted atazanavir (ATV/r) both relative to tenofovir and efavirenz. CI, confidence interval.

^aeGFR (ml/min per 1.73 m²) calculated with the Chronic Kidney Disease Collaboration (CKD-EPI) equation [13].

combine tenofovir with efavirenz. There is no evidence that this decrease then either reverses – or continues – beyond 6 months. This initial decrease relative to tenofovir with efavirenz appears worse with ATV/r than with LPV/r.

These results are consistent with results from recent randomized controlled trials and observational studies. In the Altair trial, the difference in eGFR between tenofovir with efavirenz and tenofovir with ATV/r was -4.0 ml/min per 1.73 m² at 48 weeks, but only 0.5 ml/min per 1.73 m² between 48 and 96 weeks [23]. This difference in eGFR between therapies was apparent at the first follow-up visit after only 4 weeks on therapy [23,24]. In the AIDS Clinical Trials Group 5202 trial, the difference in calculated creatinine clearance between tenofovir with efavirenz and tenofovir with ATV/r was -5.0 ml/min at 48 weeks, but only -2.5 ml/min between 48 and 96 weeks [11]. Other data from earlier observational studies are more difficult to interpret [25]. Some of these studies include both treatment-naïve and treatment-experienced patients [4,8] and all compare patients on tenofovir in protease inhibitor-sparing therapies with patients on tenofovir in protease inhibitor-based therapies, with a variety of other drugs in use in each case [4,8,9]. However, it is likely that most patients on a protease inhibitor-sparing therapy received efavirenz and most patients on a protease inhibitor-based therapy received LPV/r. These studies show differences at 48 weeks [4,8,9] that are not necessarily statistically significant [4] but always with a greater decline in GFR when tenofovir is co-administered with a protease inhibitor.

Three more recent observational studies focus on the clinical consequences of a decline in renal function. All used time to event modelling with renal impairment as their primary outcome (eGFR < 60 ml/min per 1.73 m²) – all found renal impairment more likely with exposure to boosted protease inhibitors, mostly LPV/r and ATV/r [26–28]. In each study, not all patients received tenofovir: in one study impairment was not only associated with exposure to tenofovir, but with a greater risk of impairment if tenofovir was co-administered with a protease inhibitor [26], whereas in another study

impairment was not associated with exposure to tenofovir at all [28].

Various mechanisms are suggested to explain why co-administration of tenofovir with a boosted protease inhibitor might lead to a greater decrease in glomerular filtration. LPV/r and ATV/r are known to increase plasma levels of tenofovir by between 20 and 30% [29,30]. Possible explanations for the increase in tenofovir in plasma are a higher absorption of the prodrug tenofovir disoproxil fumarate by a protease inhibitor-related inhibition of P-glycoprotein or reduced renal clearance of tenofovir due to protease inhibitor-induced drug interaction [6,31–33]. Between 20 and 30% of tenofovir is actively transported into renal proximal tubule cells by the organic anion transporters organic anion transporter 1 (OAT1) and OAT3. Subsequently, the drug is secreted into the tubular lumen by membrane transporters multidrug resistance proteins (MRPs): MRP-2 and MRP-4; these proteins are encoded by the efflux transporter genes *ABCC2* and *ABCC4* [34]. Several drugs are known to interact with these transporters and may lead to excessive entry or reduced outflow of tenofovir, thus favouring intracellular accumulation and tubular cell toxicity. Several investigators suggest that ritonavir could inhibit the active tubular secretion of tenofovir mediated by the MRP-2 transporter, leading to intracellular accumulation of the drug and toxic effects [35]. However, others suggest that tenofovir is only a substrate for MRP-4, a transporter not inhibited by ritonavir [36–38]. These mechanisms may be enhanced by host genetics. For example, a single-nucleotide polymorphism in *ABCC2* has been found in HIV-infected patients who develop tenofovir-induced nephrotoxicity [39]. ATV/r tends to crystallize in tubular cells, in rare cases leading to nephrolithiasis and interstitial nephritis [40,41]; it is not known whether intratubular crystal formation plays any role in the greater early decrease in eGFR seen among patients on tenofovir and ATV/r relative to patients on tenofovir and LPV/r.

However, the very early decreases in eGFR seen when tenofovir is co-administered with a boosted protease inhibitor might reflect a greater tenofovir-induced

inhibition of creatinine secretion in the proximal tubule, rather than a greater decline in glomerular filtration (which is what eGFR purports to measure) [42]. It is not possible to distinguish between these two alternatives in our study, but this explanation is consistent with early differences in eGFR between efavirenz and protease inhibitor-based therapies. Ultimately, persistent tenofovir-induced tubular cell injury might be expected to lead to a lower GFR [34].

Our study offers a number of advantages over previous observational studies. First, we used calibrated creatinine measurements to adjust for different measurement techniques between laboratories. Second, we compared patients only while on the specific therapies of interest, with little variation between therapies in the use of other antiretroviral drugs (with over 90% of patients receiving either lamivudine or emtricitabine as a third drug). Third, we censored follow-up if patients stop taking the therapy of interest, but then used inverse probability weights to adjust for informative censoring if, for example, patients with declining eGFR were taken off tenofovir because of this decline. Changes to the therapy of interest were common and likely to be informative in the sense that treatment failure, medication intolerance or convenience often influence the decision to switch antiretroviral drugs. The use of time-dependent censoring weights to adjust for potentially informative censoring is an important advantage of our analysis. This adjustment gives 'per protocol' estimates of the differences between therapies – differences that one would expect to see if patients were to remain on their initial therapy. This may explain why in our study we saw a slightly greater initial decline in eGFR with tenofovir and ATV/r, relative to tenofovir and efavirenz, than the decline seen in two recent randomized controlled trials. In one trial, around 30% of patients did not remain on their randomized therapy [11]; in the other, an unknown number of patients switched either from efavirenz to nevirapine or from ATV/r to another boosted protease inhibitor [24].

Our study presents some limitations. First, the sample in our main analysis represents only 55% of our population of interest, so there was clearly potential for selection bias. However, including uncalibrated creatinine measurements increased this sample to 76% of our population of interest without reducing estimates of early differences in eGFR between therapies. Second, our population of interest was a cohort in which most patients had relatively normal renal function and a low risk of rapid decline in renal function. These results may not apply to other patient populations, such as those with a higher prevalence of diabetes, hypertension or hepatitis. Third, causality is inherently difficult to establish from observational data and our estimate of the causal effect of one therapy relative to another requires correctly specified models for the two sets of weights and for the differences between therapies (see Appendix, Supplemental Digital

Content 1, <http://links.lww.com/QAD/A197>). Fourth, patients do not necessarily have the same frequency of serum creatinine measurement during follow-up and it is logical to expect that patients with declining eGFR received more frequent monitoring. However, this would not necessarily create a strong bias, unless one therapy led to a far greater decline in renal function than another. Fifth, there could be interlaboratory variation in the calibration of serum creatinine assays. This would seem unlikely to introduce bias in a comparison of specific therapies, and indeed including even uncalibrated measurements in our analyses gave similar estimates. Sixth, the different formulas used to assess glomerular filtration were all derived in HIV-negative populations and have not been validated in those with HIV [43]. Finally, routine collection of urine samples started only recently in the SHCS and, therefore, glucosuria and proteinuria could not be evaluated in this study.

Our results suggest that use of tenofovir co-administered with the boosted protease inhibitors LPV/r and ATV/r leads to an initial decrease in eGFR during the first months of therapy relative to use of tenofovir and efavirenz. Our plots (Fig. 1) are consistent with the almost immediate decline seen in a recent trial [23,24] and suggest rapid change that does not continue and indeed might be partially reversible if tenofovir were discontinued [44]. However, any recovery may be less than complete, and so while this decrease in eGFR – relative to efavirenz – may be an acceptable side-effect to many patients and their treating clinicians, its long-term clinical consequences are not yet clear, particularly for patients whose renal function is already impaired when starting therapy or for patients at risk of a greater decline in renal function, such as diabetic or hypertensive patients for whom close monitoring of renal function is crucial. Given the need for lifelong antiretroviral therapy, our data underscore the importance of long-term monitoring of renal function.

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Conflicts of interest

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The members of the Swiss HIV Cohort Study are Barth J, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Celleraï C, Egger M, Elzi L, Fehr J, Fellay J, Flepp M, Francioli P (President of the SHCS), Furrer H (Chairman of the Clinical and Laboratory Committee), Fischer M (deceased 13 December 2010.), Fux CA, Gorgievski M, Günthard H (Chairman of the Scientific Board), Haerry D (Deputy of 'Positive Council'), Hasse B, Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Keiser O, Kind C, Klimkait T, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Rauch A, Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother and Child Substudy), Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

References

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services (Updated 10 January 2011). <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>. [Accessed 12 July 2011]
- 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.
- Fux CA, Simcock M, Wolbers M, Bucher HC, Hirschel B, Opravil M, et al. **Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study.** *Antivir Ther* 2007; **12**:1165–1173.
- Buchacz K, Young B, Baker RK, Moorman A, Chmiel JS, Wood KC, et al. **Renal function in patients receiving tenofovir with ritonavir/lopinavir or ritonavir/atazanavir in the HIV Outpatient Study (HOPS) cohort.** *J Acquir Immune Defic Syndr* 2006; **43**:626–628.
- Cihlar T, Ray AS, Laflamme G, Vela JE, Tong L, Fuller MD, et al. **Molecular assessment of the potential for renal drug interactions between tenofovir and HIV protease inhibitors.** *Antivir Ther* 2007; **12**:267–272.
- Kiser JJ, Carten ML, Aquilante CL, Anderson PL, Wolfe P, King TM, et al. **The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients.** *Clin Pharmacol Ther* 2008; **83**:265–272.
- Ray AS, Wright MR, Rhodes GR. **Lack of evidence for an effect of lopinavir/ritonavir on tenofovir renal clearance.** *Clin Pharmacol Ther* 2008; **84**:660.
- 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.
- Gallant JE, Moore RD. **Renal function with use of a tenofovir-containing initial antiretroviral regimen.** *AIDS* 2009; **23**:1971–1975.
- Mocroft A, Kirk O, Reiss P, De WS, 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.
- 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.** *Ann Intern Med* 2011; **154**:445–456.
- Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Günthard HF, Telenti A, et al. **Cohort profile: the Swiss HIV Cohort study.** *Int J Epidemiol* 2010; **39**:1179–1189.
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, et al. **A new equation to estimate glomerular filtration rate.** *Ann Intern Med* 2009; **150**:604–612.
- Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. **Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate.** *Ann Intern Med* 2006; **145**:247–254.
- Cockcroft DW, Gault MH. **Prediction of creatinine clearance from serum creatinine.** *Nephron* 1976; **16**:31–41.
- Cole SR, Hernan MA, Margolick JB, Cohen MH, Robins JM. **Marginal structural models for estimating the effect of highly active antiretroviral therapy initiation on CD4 cell count.** *Am J Epidemiol* 2005; **162**:471–478.
- Hernan MA, Brumback BA, Robins JM. **Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures.** *Stat Med* 2002; **21**:1689–1709.
- 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.
- Cole SR, Hernan MA. **Constructing inverse probability weights for marginal structural models.** *Am J Epidemiol* 2008; **168**:656–664.
- Robins JM, Hernan MA, Brumback B. **Marginal structural models and causal inference in epidemiology.** *Epidemiology* 2000; **11**:550–560.
- Liang KY, Zeger SL. **Longitudinal data analysis using generalized linear models.** *Biometrika* 1986; **73**:13–22.
- Wickham H. *ggplot2: elegant graphics for data analysis.* New York: Springer; 2009.
- Dazo C, Fahey P, Puls RL, Winston A, Boesecke C, Avhingsanon A, et al. **Small but significant and nonprogressive decline in glomerular filtration rate is observed in therapy naive HIV-positive subjects commencing ritonavir-boosted atazanavir (r/ATV), compared to either efavirenz (EFV) or zidovudine/abacavir (ZDV/ABC) all with tenofovir (TDF)/emtricitabine (FTC) after 48 weeks, a randomised controlled study [abstract O-178].** In: *18th Conference on Retroviruses and Opportunistic Infections*; 2011.
- Puls RL, Srasuebkul P, Petoumenos K, Boesecke C, Duncombe C, Bellosso WH, et al. **Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study.** *Clin Infect Dis* 2010; **51**:855–864.
- Flandre P. **Tenofovir and changes in renal function.** *AIDS* 2010; **24**:619–620.
- Morlat P, Vivot A, Dauchy F, Asselinaeu J, Vandenhende MA, Lazaro E, et al. **Antiretroviral drugs and incidence of chronic kidney disease, ANRS CO3 Aquitaine Cohort, France, 2004–2008 [abstract WEPDB0104].** In: *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*; 2011.
- Rockwood N, Mandalia S, Sirokosta J, Jones R, Boffito M, Gazzard B, et al. **A comparative analysis of risk factors associated with efavirenz, darunavir/ritonavir, lopinavir/ritonavir, atazanavir/ritonavir and renal impairment [abstract TUPE250].** In: *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*; 2011.
- Hosein SR, Johns K, Chan K, Raboud J, Harrs M, Milan D, et al. **Progression to impaired estimated glomerular filtration rate (eGFR) between antiretroviral therapy regimens in the Canadian Observational Cohort (CANOC) collaboration [abstract TUPE254].** In: *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*; 2011.
- 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.

30. Bristol-Myers Squibb. Reyataz (atazanavir sulfate): prescribing information. (updated February 2011). http://packageinserts.bms.com/pi/pi_reyataz.pdf. [Accessed 3 September 11]
31. Perloff ES, Duan SX, Skolnik PR, Greenblatt DJ, von Moltke LL. **Atazanavir: effects on P-glycoprotein transport and CYP3A metabolism in vitro.** *Drug Metab Dispos* 2005; **33**:764–770.
32. van Heeswijk RP, Bourbeau M, Campbell P, Seguin I, Chauhan BM, Foster BC, *et al.* **Time-dependent interaction between lopinavir/ritonavir and fexofenadine.** *J Clin Pharmacol* 2006; **46**:758–767.
33. Ding R, Tayrouz Y, Riedel KD, Burhenne J, Weiss J, Mikus G, *et al.* **Substantial pharmacokinetic interaction between digoxin and ritonavir in healthy volunteers.** *Clin Pharmacol Ther* 2004; **76**:73–84.
34. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, Sanchez-Nino MD, Izquierdo MC, Poveda J, *et al.* **Tenofovir nephrotoxicity: 2011 update.** *AIDS Res Treat* 2011; **2011**:354908.
35. Izzedine H, Launay-Vacher V, Deray G. **Antiviral drug-induced nephrotoxicity.** *Am J Kidney Dis* 2005; **45**:804–817.
36. Ray AS, Cihlar T, Robinson KL, Tong L, Vela JE, Fuller MD, *et al.* **Mechanism of active renal tubular efflux of tenofovir.** *Antimicrob Agents Chemother* 2006; **50**:3297–3304.
37. Imaoka T, Kusuhara H, Adachi M, Schuetz JD, Takeuchi K, Sugiyama Y. **Functional involvement of multidrug resistance-associated protein 4 (MRP4/ABCC4) in the renal elimination of the antiviral drugs adefovir and tenofovir.** *Mol Pharmacol* 2007; **71**:619–627.
38. Kohler JJ, Hosseini SH, Green E, Abuin A, Ludaway T, Russ R, *et al.* **Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters.** *Lab Invest* 2011; **91**:852–858.
39. Izzedine H, Hulot JS, Villard E, Goyenvalle C, Dominguez S, Ghosn J, *et al.* **Association between ABCC2 gene haplotypes and tenofovir-induced proximal tubulopathy.** *J Infect Dis* 2006; **194**:1481–1491.
40. Couzigou C, Daudon M, Meynard JL, Borsa-Lebas F, Higuieret D, Escaut L, *et al.* **Urolithiasis in HIV-positive patients treated with atazanavir.** *Clin Infect Dis* 2007; **45**:e105–e108.
41. Izzedine H, M'rad MB, Bardier A, Daudon M, Salmon D. **Atazanavir crystal nephropathy.** *AIDS* 2007; **21**:2357–2358.
42. Vrouenraets SM, Fux CA, Wit FW, Garcia EF, Furrer H, Brinkman K, *et al.* **Persistent decline in estimated but not measured glomerular filtration rate on tenofovir may reflect tubular rather than glomerular toxicity.** *AIDS* 2011; **25**:2149–2155.
43. Mocroft A. **The difficulties of classifying renal disease in HIV-infected patients.** *HIV Med* 2011; **12**:1–3.
44. Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D'Agati VD, Markowitz GS. **Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities.** *Kidney Int* 2010; **78**:1171–1177.