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

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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 \(-2.6\text{ ml/min per 1.73 m}^2\) (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 m\(^2\) (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 \(-7.6\text{ ml/min per 1.73 m}^2\) (95\% CI \(-11.8\) to \(-3.4\)) during the first 6 months of therapy, then followed by a difference of \(-0.5\text{ ml/min per 1.73 m}^2\) (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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Keywords: HAART, HIV, kidney glomerulus, proximal kidney tubules

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 \cite{1}. Tenofovir is mainly eliminated by the kidneys and its use is associated with reduced renal function \cite{2}. Regular monitoring of

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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-naive patients starting first therapy with tenofovir and either efavirenz or ritonavir-boosted lopinavir (LPV/r) or ritonavir-boosted atazanavir (ATV/r), 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, 1053 (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 109, 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

<p>| Table 1. Patient flow for those starting first therapy with co-administered tenofovir. |
|-------------------------------------------------|-----|-----|-----|</p>
<table>
<thead>
<tr>
<th>Efavirenz</th>
<th>LPV/r</th>
<th>ATV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients starting after 1 January 2002</td>
<td>909</td>
<td>451</td>
</tr>
<tr>
<td>Patients with ≥1 calibrated or uncalibrated creatinine measurement after starting therapy (%)</td>
<td>84</td>
<td>83</td>
</tr>
<tr>
<td>Along with HIV RNA and CD4⁺ T-cell count within 6 months before starting therapy (%) (sensitivity analysis)</td>
<td>78</td>
<td>68</td>
</tr>
<tr>
<td>Patients with ≥1 calibrated creatinine measurement after starting therapy (%)</td>
<td>57</td>
<td>73</td>
</tr>
<tr>
<td>Along with HIV RNA and CD4⁺ T-cell count within 6 months before starting therapy (%) (main analysis)</td>
<td>53</td>
<td>60</td>
</tr>
<tr>
<td>Number of patients in the main analysis</td>
<td>484</td>
<td>269</td>
</tr>
<tr>
<td>With a calibrated creatinine measurement within 6 months before starting therapy (%)</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Last eGFR before starting therapy (ml/min per 1.73 m²)</td>
<td>105 (92–116)</td>
<td>108 (98–117)</td>
</tr>
<tr>
<td>First eGFR after starting therapy (ml/min per 1.73 m²)</td>
<td>105 (94–114)</td>
<td>102 (88–112)</td>
</tr>
<tr>
<td>Time between these two eGFRs (months)</td>
<td>Median (IQR) 5 (3–6)</td>
<td>5 (2–7)</td>
</tr>
<tr>
<td>Followed until b</td>
<td>Administrative censoring (%)</td>
<td>61</td>
</tr>
<tr>
<td>Patient dropped out of SHCS (%)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Patient stopped taking tenofovir (%)</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Patient stopped taking efavirenz, LPV/r or ATV/r (%)</td>
<td>33</td>
<td>56</td>
</tr>
<tr>
<td>Time to administrative censoring (months)</td>
<td>Median (IQR) 28 (11–50)</td>
<td>28 (14–46)</td>
</tr>
<tr>
<td>Time to patient dropped out of SHCS (months)</td>
<td>Median (IQR) 10 (6–48)</td>
<td>14 (1–26)</td>
</tr>
<tr>
<td>Time to patient stopped taking tenofovir (months)</td>
<td>Median (IQR) 12 (6–26)</td>
<td>12 (4–22)</td>
</tr>
<tr>
<td>Time to patient stopped taking efavirenz, LPV/r or ATV/r (months)</td>
<td>Median (IQR) 12 (5–24)</td>
<td>9 (5–15)</td>
</tr>
</tbody>
</table>

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) before and after starting therapy, if known, and length of follow-up, IQR, interquartile range; SHCS, Swiss HIV Cohort Study.

*Estimated glomerular filtration rate (ml/min per 1.73 m²) 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).
Sensitivity analyses

Estimated differences between therapies appear robust to outliers. After excluding values of eGFR below 30 mL/min per 1.73 m^2, the estimated difference in eGFR during the first 6 months of therapy was −2.9 mL/min per 1.73 m^2 (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 m^2 (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
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...
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 \(-4.0 \text{ ml/min per } 1.73 \text{ m}^2\) at 48 weeks, but only \(0.5 \text{ ml/min per } 1.73 \text{ m}^2\) 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 \text{ ml/min at } 48 \text{ weeks, but only } -2.5 \text{ ml/min between } 48 \text{ and } 96 \text{ weeks} [11]. Other data from earlier observational studies are more difficult to interpret [25]. Some of these studies include both treatment-naive and treatment-experienced patients [4,8] and all compare patients on tenofovir in protease inhibitor-sparring 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-sparring 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] but 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 \textit{ABCC}2 and \textit{ABCC}4 [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 \textit{ABCC}2 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

### Table 3. Difference in average estimated glomerular filtration rate.

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

Differences in eGFR* 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.

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