Low incidence of renal impairment observed in tenofovir-treated patients

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Objectives: To compare the incidence of renal impairment in HIV-infected patients exposed versus unexposed to tenofovir and to characterize risk factors associated with renal impairment.

Methods: We undertook a retrospective cohort and nested case–control study of 514 Northwestern University HIV Outpatient Study participants who received antiretroviral therapy (ART) between 1 August 2001 and 31 July 2007. Renal impairment was defined as meeting at least one of two validated criteria based on serum creatinine, calculated glomerular filtration rate and creatinine clearance. Multivariable analysis was performed to identify risk factors for renal impairment.

Results: Renal impairment occurred in 14% (n = 72) of the cohort and was not correlated with exposure to tenofovir in univariate analyses. In multivariable analysis, more advanced age [odds ratio (OR) = 1.04, P = 0.02], diabetes (OR = 3.6, P < 0.01), decreased weight (OR = 0.97, P = 0.02) and endpoint CD4 ≤200 cells/mm3 (OR = 2.5, P = 0.03) were positive predictors of renal impairment; tenofovir exposure (OR = 0.41, P = 0.01) was negatively correlated with renal impairment.

Conclusions: Tenofovir-containing ART was associated with less renal impairment than ART without tenofovir in a patient cohort with a high incidence of renal impairment. Chronic co-morbid conditions known to be associated with renal impairment should be excluded prior to attributing renal impairment to tenofovir.

Keywords: antiretroviral therapy, nephrotoxicity, risk factors, HIV/AIDS

Introduction

Tenofovir, a preferred component of antiretroviral therapy (ART) for treatment-naive patients, exhibits potent antiviral activity, is well tolerated and is easy to administer.1,2 However, concern over its association with renal impairment exists.3–6 Despite conflicting reports on the extent and incidence of renal dysfunction, some clinicians are reluctant to prescribe tenofovir for patients with baseline renal insufficiency.

Although structurally related to cidofovir and adefovir, two antivirals with dose-limiting nephrotoxicity,15,16 the incidence of adverse renal events associated with tenofovir was initially reported to be no higher than that associated with comparator nucleoside reverse transcriptase inhibitors.17–19 However, post-marketing cases of acute renal failure, Fanconi syndrome and nephrogenic diabetes insipidus have been reported.17–20 Acute tubular necrosis appears to be the mechanism, occasionally resulting in irreversible loss of renal function.3–6

Previous studies have identified potential risk factors for renal impairment among persons receiving tenofovir, including pre-existing renal disease,1 being ART-naive at the time of tenofovir initiation,2 diabetes mellitus,9 advanced age,14 hypertension,14 having a baseline CD4+ cell count (CD4) <50 or 200 cells/mm317,20–22 and simultaneous use of tenofovir and ritonavir.7,11,23

An open-label, randomized study conducted among ART-naive patients comparing abacavir/ lamivudine and tenofovir/emtricitabine, both co-prescribed with efavirenz, found no differences in calculated glomerular filtration rates (GFR) over time but noted increases in markers of tubular dysfunction in the tenofovir/emtricitabine arm.24 However, among diverse ‘real world’, ART-experienced patients, it is unclear how much renal impairment is attributable to tenofovir use versus other co-existing risks, including HIV and chronic co-morbidities.25,26 We compared the incidence of renal impairment in a large cohort of HIV-infected patients who received ART with or without tenofovir. Additionally, we sought to evaluate non-ART risk factors for renal impairment.
Methods

This was a retrospective cohort study of HIV-infected patients enrolled in the Northwestern University HIV Outpatient Study (HOPS), an ongoing cohort that has enrolled over 8000 patients at 10 clinic sites in the USA since its inception in 1993. Study personnel abstract clinical information and laboratory data into the electronic HOPS database after each clinic visit. All HOPS participants provide written informed consent and the study is reviewed annually by the Northwestern University Institutional Review Board.

All patients in the Northwestern HOPS who received ART at any time during the study period (1 August 2001 to 31 July 2007) were eligible. Patients were excluded if data necessary to evaluate the primary outcome or risk factors for renal impairment were missing (outlined below). Additional exclusion criteria included renal impairment at baseline or having documented nephrolithiasis.

Outcome measures

The primary endpoint, renal impairment, was defined as meeting at least one of two criteria: (i) GFR \( \leq 60 \text{ mL/min/1.73 m}^2 \) on two consecutive measurements [calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation], which constitutes stage 3 or greater renal disease according to the Kidney Disease Outcomes Quality Initiative (K/DOQI); (ii) a \( \geq 2 \)-fold increase in serum creatinine (SCR) above baseline or a \( \geq 50\% \) decline in creatinine clearance (CrCl) from baseline on one or more measurements, which meets the definition of ‘renal injury’ by the risk, injury, failure, loss and end-stage kidney (RIFLE) criteria. For this criterion, CrCl was calculated using the Cockcroft–Gault equation and the patient’s actual body weight. The baseline SCR was defined as the first recorded SCR during the study period. The study endpoint was defined as a patient’s first renal impairment event or the date at which the last available SCR value prior to 1 August 2007 was obtained.

Study group assignment based on tenofovir exposure

In order to minimize bias due to tenofovir discontinuation in patients with new onset renal impairment, any patient who received tenofovir prior to developing renal impairment was characterized as tenofovir exposed. Patients were characterized as tenofovir unexposed if they did not receive tenofovir during the study period, if they experienced renal impairment prior to initiating tenofovir or if their most recent laboratory data were obtained before the first receipt of tenofovir.

Data collection

The following clinical and laboratory data were collected: age, sex, race, CD4, HIV-1 RNA level (viral load; VL), SCR, weight, ART start and stop dates, use of nephrotoxic medications, and non-AIDS co-morbidities (hypertension, diabetes, nephrolithiasis and hepatitis B or C). If patients were still receiving ART at the end of study follow-up, then 31 July 2007 was used as the ART stop date. Nephrotoxic medications included angiotensin-converting enzyme inhibitors, amphotericin B, foscarnet, colistin, tacrolimus and cyclosporine. CrCl and GFR were calculated for each available SCR value using the closest age and weight. Age and weight values nearest in time to the study endpoint were used to assess associations with renal impairment. Baseline and endpoint CD4 and log-transformed VL were defined as those values measured closest to the date of the baseline and endpoint SCR, respectively. To further characterize associations between HIV disease stage and renal impairment, data regarding the proportion of patients with a CD4 \( \leq 200 \text{ cells/mm}^3 \), an undetectable VL (\( \leq 50 \text{ copies/mL} \)) and a VL \( >5.0 \log_{10} \text{ copies/mL} \) were evaluated.

Nested case–control analysis

In order to more precisely identify risk factors for renal impairment within the cohort, a nested case–control analysis was performed. A case was defined as any patient who met the composite definition of renal impairment during the study period. Controls were randomly selected in a 1:2 case:control ratio.

Statistical analyses

All patients enrolled into the Northwestern HOPS were screened for inclusion, comprising a sample size of convenience. Statistical analyses were performed to assess potential differences between patients who developed renal impairment versus those who did not, as well as to detect baseline differences between patients exposed versus not exposed to tenofovir in both the total cohort, as well as the nested case–control group.

The \( \chi^2 \) test was used to evaluate the significance of associations between renal impairment and tenofovir exposure, and between categorical variables and renal impairment or tenofovir exposure. Associations between continuous variables for both renal impairment and tenofovir exposure were evaluated using Student’s t-test for unrelated samples. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated with multiple logistic regression.

The multiple logistic regression model was developed for the case–control group to evaluate the association between renal impairment and patient characteristics. The initial model included all variables that were associated with the outcome (P value \( \leq 0.1 \)) by univariate analysis (see Table 4) or had biological plausibility for tenofovir use or renal impairment, specifically baseline SCR, hepatitis B virus co-infection, and baseline or endpoint VL >5.0 log_{10} copies/mL. Neither CrCl nor GFR was included, as these calculated values are based upon SCR, weight and age, all of which were included. Backward conditional techniques were used to determine the most explanatory model. All statistical analyses were performed with SPSS version 18.0 (SPSS, Inc., Somers, NY, USA).

Results

Out of 562 patients screened, 48 were excluded: 18 had incomplete information (4 with missing demographics, 14 with no baseline and subsequent SCR measurements); 29 patients met criteria for renal impairment at baseline; and one patient was diagnosed with indinavir-related nephrolithiasis. Therefore, 514 patients were included. Mean follow-up was 44.3 months (SD = 23.8 months), and mean age was 46.1 years (range 22–76 years, SD = 8.9 years). Study participants were predominantly male (80.5%) and Caucasian (59.7%). Mean baseline CD4 was 433 cells/mm\(^3\) (SD = 259 cells/mm\(^3\)), and mean baseline VL was 2.0 log_{10} copies/mL (SD = 2.0 log_{10} copies/mL).

Seventy-two patients (14.0%) developed renal impairment during the study period. Comparisons between patients who did versus did not develop renal impairment are presented in Table 1.

Sixty-eight percent of patients (n = 348) received tenofovir for a mean duration of 23.2 months (SD = 17.5 months). In this group, the incidence of renal impairment was 12.1%, which was similar to that observed in the overall cohort. Only five patients developed renal impairment after tenofovir discontinuation (an average of 12.4 months after, range 2.1–23 months).

Table 2 compares persons exposed versus not exposed to tenofovir. Those who received tenofovir had a significantly greater mean baseline CrCl. More patients unexposed to tenofovir developed renal impairment by the K/DOQI criteria (GFR <60 mL/min/1.73 m\(^3\)), but only non-significant trends in this
direction were observed when considering the RIFLE criterion or the composite renal impairment outcome (Table 3).

**Nested case–control analysis**

The results of the nested case–control analysis (cases, \(n = 72\); controls, \(n = 144\)) are presented in Table 4. Factors positively associated with renal impairment included more advanced age, lower weight, hypertension, diabetes mellitus, use of concomitant nephrotoxic medications, lower mean CD4 and higher mean VL at endpoint. Baseline differences in renal function were also observed. Finally, tenofovir-exposed patients were less likely to demonstrate renal impairment \((P < 0.01)\).

Following multivariable analysis (Table 5), more advanced age, diabetes and endpoint CD4 \(\leq 200\) cells/mm\(^3\) were positively associated with renal impairment; tenofovir exposure and higher weight were negatively associated with renal impairment.

**Discussion**

In this prospectively followed cohort of HIV-infected outpatients, we found a negative correlation between tenofovir use and renal

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics of those who did or did not meet the definition of renal impairment ((n = 514))</th>
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</thead>
<tbody>
<tr>
<td>Renal impairment ((n = 72))</td>
</tr>
<tr>
<td>Age (years)(^a)</td>
</tr>
<tr>
<td>Male sex(^b)</td>
</tr>
<tr>
<td>Race(^b)</td>
</tr>
<tr>
<td>white</td>
</tr>
<tr>
<td>black</td>
</tr>
<tr>
<td>other</td>
</tr>
<tr>
<td>Weight (kg)(^c)</td>
</tr>
<tr>
<td>Hypertension(^b)</td>
</tr>
<tr>
<td>Diabetes(^b)</td>
</tr>
<tr>
<td>Hepatitis B co-infection(^b)</td>
</tr>
<tr>
<td>Hepatitis C co-infection(^b)</td>
</tr>
<tr>
<td>Nephrotoxic drugs(^b,c)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm(^3))</td>
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<tr>
<td>baseline (\leq 200) at baseline(^b)</td>
</tr>
<tr>
<td>endpoint (\leq 200) at endpoint(^b)</td>
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<tr>
<td>HIV-1 RNA level</td>
</tr>
<tr>
<td>baseline (\leq 50) copies/mL(^b)</td>
</tr>
<tr>
<td>endpoint (&gt; 5 \log_{10}) copies/mL(^b)</td>
</tr>
<tr>
<td>SCR ((\mu)mol/L)(^a)</td>
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<tr>
<td>baseline</td>
</tr>
<tr>
<td>CRCL (mL/min)(^a)</td>
</tr>
<tr>
<td>baseline</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m(^2))(^a)</td>
</tr>
<tr>
<td>baseline</td>
</tr>
<tr>
<td>Protease inhibitor exposure(^b,c)</td>
</tr>
<tr>
<td>Tenofovir use(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Values reported as mean (SD), compared using Student’s \(t\)-test.  
\(^b\)Values reported as number of patients (%), compared using \(\chi^2\) test.  
\(^c\)Characterized at study endpoint.
Table 2. Selected patient characteristics of those exposed versus not exposed to tenofovir (n = 514)

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir (n = 348)</th>
<th>No tenofovir (n = 166)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensiona</td>
<td>88 (25.3%)</td>
<td>36 (21.7%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetesa</td>
<td>33 (9.5%)</td>
<td>11 (6.6%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Hepatitis B co-infectiona</td>
<td>25 (7.2%)</td>
<td>7 (4.2%)</td>
<td>0.19</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)a ≤200 at baseline</td>
<td>64 (18.4%)</td>
<td>30 (18.1%)</td>
<td>0.93</td>
</tr>
<tr>
<td>≤200 at endpoint</td>
<td>58 (16.7%)</td>
<td>23 (13.9%)</td>
<td>0.41</td>
</tr>
<tr>
<td>HIV-1 RNA levela</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline ≤50 copies/mL</td>
<td>146 (42.0%)</td>
<td>89 (53.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>endpoint ≤50 copies/mL</td>
<td>233 (67.0%)</td>
<td>86 (51.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baseline CRCL (mL/min)b</td>
<td>107.7 (15.4)</td>
<td>103.7 (18.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Endpoint CRCL (mL/min)b</td>
<td>96.8 (22.2)</td>
<td>92.6 (25.3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

aValues reported as number of patients (%), compared using χ² test.
bValues reported as mean (SD), compared using Student’s t-test.

Table 3. Renal impairment between patients exposed to tenofovir and those not exposed to tenofovir (n = 514)

<table>
<thead>
<tr>
<th>Criteria for renal impairment</th>
<th>Tenofovir exposure (n = 348)</th>
<th>No tenofovir exposure (n = 166)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>K/DOQIa</td>
<td>32 (9.2%)</td>
<td>27 (16.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>RIFLEb</td>
<td>21 (6.0%)</td>
<td>15 (9.0%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Composite outcomec</td>
<td>42 (12.1%)</td>
<td>30 (18.1%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Data are presented as number of patients (%), compared using χ² test.

- K/DOQI: Kidney Disease Outcomes Quality Initiative: GFR < 60 mL/min/1.73 m² by the abbreviated MDRD equation.
- RIFLE: Risk of renal dysfunction; Injury to the kidney; Failure of kidney function.
- Composite: Loss of kidney function and End-stage kidney disease: ≥2-fold increase in SCR above baseline or a ≥50% decline in creatinine clearance from study-defined baseline.
- Patient met one or more of the defined criteria for renal impairment during the study period.

improvement. In nested case–control analyses, tenofovir recipients were 59% less likely to develop renal impairment than non-tenofovir recipients. Tenofovir use was associated with very modest renal impairment, consonant with existing data suggesting that overt tenofovir-associated nephrotoxicity appears uncommon.4–12,14 Minor, often clinically insignificant decreases in CRCL or GFR associated with tenofovir have more commonly been reported.12–14,20,23,32–36

A recently published large, retrospective cohort analysis of treatment-naive patients found a small but statistically significant GFR decline over 104 weeks among tenofovir recipients when compared with tenofovir-unexposed persons (mean estimate, −7.6 mL/min/1.73 m², P < 0.001).37 Tenofovir-exposed patients had a greater risk of proximal tubular dysfunction (adjusted hazard ratio (HR) 5.23; 95% CI 2.08–13.1), yet there was no significant difference in ‘incident nephrotoxicity’ (GFR decrease of >50% from baseline, adjusted HR 1.63; 95% CI 0.96–2.76) or SCR increase of >176.8 μmol/L (adjusted HR 1.65; 95% CI 0.85–3.20). In contrast, in our study both tenofovir-exposed and unexposed patients had similar baseline and endpoint mean GFR, though tenofovir recipients had higher baseline CRCL and a trend towards higher endpoint CRCL. Also, we observed less risk of incident renal impairment in the tenofovir-exposed group. However, in our study specific criteria used to measure proximal tubular dysfunction were not available.

While Horberg et al.37 only enrolled patients whose first ART regimen included tenofovir, our study included ART-experienced patients, many of whom first initiated tenofovir beyond their initial regimen. In addition, our cohort was arguably at higher risk of renal impairment because of more prevalent co-morbidities (diabetes, hypertension, hepatitis).

In comparisons of HIV suppression and immune function between study groups, tenofovir-exposed patients had a higher baseline VL but achieved better viral suppression than tenofovir-unexposed patients. While this supports data from prospective randomized trials that suggest tenofovir-containing ART are more potent than regimens without tenofovir, we did not evaluate antiretrovirals co-prescribed with tenofovir, so this observed benefit cannot be attributed to tenofovir alone. However, enhanced HIV suppression may partially explain the negative correlation of tenofovir with renal impairment. Similarly, in a prospective observational study of 99 patients treated with versus without tenofovir, no significant GFR changes over 48 weeks were observed (−1.5 versus −1.6 mL/min, P = NS).38 The subset of tenofovir-exposed persons whose HIV suppression improved also achieved significant improvements in GFR (+8.4 mL/min) compared with persons whose degree of HIV suppression was unchanged or worsened (−1.0 and −4.6 mL/min, respectively, \( P < 0.01 \)).38 GFR improvements in patients with baseline renal impairment (+4.9 mL/min/1.73 m² for every 10 mL/min/1.73 m² lower baseline GFR, \( P < 0.01 \)) were also observed in a recent trial of 3316 African patients who initiated ART.39

Our findings reinforce the importance of optimal HIV control in the prevention of renal impairment. In multi-variable analysis, patients with a lower CD4 (<200 cells/mm³) were 2.5 times more likely to develop renal impairment than persons with better immune function. Although a suppressed endpoint VL was negatively associated with renal impairment development in univariate analyses, viral suppression at baseline was not overtly protective. Nevertheless, it remains plausible that the direct pathogenic effects of HIV on the kidney contributed to observed renal impairment development.

ART-treated patients have concomitant risk factors for renal impairment, including HIV itself. HIV-associated nephropathy (HIVAN) occurs more frequently among persistently viraemic persons, presumably as a consequence (at least in part) of viraemia-induced chronic inflammation.40 Recent data suggest that while rates of HIVAN have declined in the ART era,41 hypertensive and diabetic nephropathies have increased.41,42 In our cohort, 14% of patients developed renal impairment, consistent with reported incidences of other forms of kidney disease, and we found that diabetic patients were 3.6 times more likely to develop renal impairment than non-diabetic patients. It is known that up to 30% of HIV-infected persons exhibit protei
		

developed renal impairment had lower mean baseline CR\textsubscript{CL} and GFR than patients who did not develop renal impairment.

There are several limitations to our study. It is possible that the decreased risk of renal impairment observed among tenofovir-exposed persons was indicative of prescribing bias; perhaps patients perceived to be at higher risk of kidney disease were not prescribed tenofovir. Although mean baseline CR\textsubscript{CL} was higher in tenofovir-exposed persons, the absolute differences (107.7 mL/min versus 103.7 mL/min) were arguably of little clinical significance and there were no apparent differences between these groups with regard to age, rates of hypertension, diabetes or use of nephrotoxic medications. This study did not control for duration of HIV infection or extent of ART experience. It is possible that highly ART-experienced patients with longer durations of HIV infection may be at greater risk of renal impairment regardless of tenofovir exposure; however, no studies to date have found this association. Information regarding tenofovir doses prescribed and renal dose adjustments was also not available. However, if inappropriate tenofovir dosing resulted in excess drug-related toxicity, our analysis would have been biased towards finding an association between tenofovir and renal impairment. Furthermore, since

\begin{table}
\centering
\caption{Nested case–control analysis of patients with renal impairment versus those without renal impairment}
\begin{tabular}{llll}
\hline
 & Cases (n=72) & Controls (n=144) & \textit{P} value \\
\hline
Age (years)\textsuperscript{a} & 49.5 (11.2) & 46.1 (8.8) & 0.02 \\
Male sex\textsuperscript{b} & 56 (77.8\%) & 115 (79.9\%) & 0.72 \\
Race\textsuperscript{b} & & & 0.81 \\
white & 44 (61.1\%) & 83 (57.6\%) & \\
black & 21 (29.2\%) & 43 (29.9\%) & \\
other & 7 (9.7\%) & 18 (12.5\%) & \\
Weight (kg)\textsuperscript{a,c} & 76.0 (14.5) & 81.1 (16.6) & 0.03 \\
Hypertension\textsuperscript{b} & 29 (40.3\%) & 38 (26.4\%) & 0.04 \\
Diabetes\textsuperscript{b} & 17 (23.6\%) & 13 (9.0\%) & <0.01 \\
Hepatitis B co-infection\textsuperscript{b} & 5 (6.9\%) & 9 (6.3\%) & 1.00 \\
Hepatitis C co-infection\textsuperscript{b} & 12 (16.7\%) & 19 (13.2\%) & 0.49 \\
Nephrotoxic drugs\textsuperscript{b,c} & 10 (13.9\%) & 7 (4.9\%) & 0.02 \\
CD4 cell count (cells/mm\textsuperscript{3}) & & & \\
baseline\textsuperscript{a} & 374.0 (255.0) & 439.7 (247.7) & 0.07 \\
\leq 200 at baseline\textsuperscript{b} & 19 (26.4\%) & 23 (16.0\%) & 0.07 \\
endpoint\textsuperscript{a} & 352.3 (286.6) & 507.1 (312.7) & <0.01 \\
\leq 200 at endpoint\textsuperscript{b} & 20 (27.8\%) & 16 (11.1\%) & <0.01 \\
HIV-1 RNA level & & & \\
baseline mean (log\textsubscript{10} copies/mL)\textsuperscript{a} & 2.34 (2.05) & 1.84 (2.03) & 0.09 \\
\leq 50 copies/mL\textsuperscript{b} & 27 (37.5\%) & 72 (50.0\%) & 0.08 \\
> 5 log\textsubscript{10} copies/mL\textsuperscript{b} & 7 (9.7\%) & 12 (8.3\%) & 0.73 \\
endpoint mean (log\textsubscript{10} copies/mL)\textsuperscript{a} & 1.68 (2.03) & 1.12 (1.86) & 0.05 \\
\leq 50 copies/mL\textsuperscript{b} & 40 (55.6\%) & 103 (71.5\%) & 0.02 \\
> 5 log\textsubscript{10} copies/mL\textsuperscript{b} & 4 (5.6\%) & 11 (7.6\%) & 0.78 \\
SCR (\textmu mol/L)\textsuperscript{a} & & & \\
baseline & 85.0 (24.9) & 80.0 (16.1) & 0.12 \\
endpoint & 172.3 (159.3) & 83.7 (15.5) & <0.01 \\
CR\textsubscript{CL} (mL/min)\textsuperscript{a} & & & \\
baseline & 95.4 (20.7) & 108.6 (14.4) & <0.01 \\
endpoint & 59.4 (21.3) & 102.6 (17.8) & <0.01 \\
GFR (mL/min/1.73 m\textsuperscript{2})\textsuperscript{a} & & & \\
baseline & 89.5 (22.1) & 98.9 (16.0) & <0.01 \\
endpoint & 51.8 (18.8) & 92.7 (17.7) & <0.01 \\
Protease inhibitor exposure\textsuperscript{b,c} & 48 (66.7\%) & 84 (58.3\%) & 0.24 \\
Tenofovir use\textsuperscript{b} & 42 (58.3\%) & 111 (77.1\%) & <0.01 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}Values reported as mean (SD), compared using Student’s t-test.
\textsuperscript{b}Values reported as number of patients (%), compared using \chi\textsuperscript{2} test.
\textsuperscript{c}Characterized at study endpoint.
patients with baseline renal dysfunction were excluded, patients who required tenofovir dose reduction at baseline were excluded. There are also several nephrotoxic medications not captured in the HOPS database for which our analysis could not control.

In conclusion, renal impairment was common in this cohort but most commonly associated with non-HIV chronic co-morbid conditions known to predispose to kidney disease, including diabetes. Variables associated with poorer HIV control, such as lower CD4 and uncontrolled viremia, were also associated with renal impairment. The lower incidence of renal impairment noted among tenofovir-exposed patients may have been linked to improved rates of HIV suppression. Our study corroborates findings from other cohorts that suggest tenofovir-associated renal impairment has a low incidence. Hence, vigilance should be exercised in monitoring renal function and managing chronic non-HIV-related co-morbid conditions such as hypertension and diabetes. Such actions could enhance kidney health and prevent the withholding of effective ART for those with limited HIV treatment options.

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Transparency declarations
None to declare.

Author contributions
All authors were involved in study design, data analysis, and manuscript preparation. Statistical analyses were performed by K. K. S.

References


