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SHORT COMMUNICATION

The rate of recovery in renal function when patients with HIV infection discontinue treatment with tenofovir

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Objectives

Tenofovir is associated with reduced renal function. It is not clear whether patients can be expected to fully recover their renal function if tenofovir is discontinued.

Methods

We calculated the estimated glomerular filtration rate (eGFR) for patients in the Swiss HIV Cohort Study remaining on tenofovir for at least 1 year after starting a first antiretroviral therapy regimen with tenofovir and either efavirenz or the ritonavir-boosted protease inhibitor lopinavir, atazanavir or darunavir. We estimated the difference in eGFR slope between those who discontinued tenofovir after 1 year and those who remained on tenofovir.

Results

A total of 1049 patients on tenofovir for at least 1 year were then followed for a median of 26 months, during which time 259 patients (25%) discontinued tenofovir. After 1 year on tenofovir, the difference in eGFR between those starting with efavirenz and those starting with lopinavir, atazanavir and darunavir was – 0.7 [95% confidence interval (CI) –2.3 to 0.8], –1.4 (95% CI –3.2 to 0.3) and 0.0 (95% CI –1.7 to 1.7) mL/min/1.73 m^2, respectively. The estimated linear rate of decline in eGFR on tenofovir was –1.1 (95% CI –1.5 to –0.8) mL/min/1.73 m^2 per year and its recovery after discontinuing tenofovir was 2.1 (95% CI 1.3 to 2.9) mL/min/1.73 m^2 per year. Patients starting tenofovir with either lopinavir or atazanavir appeared to have the same rates of decline and recovery as those starting tenofovir with efavirenz.

Conclusions

If patients discontinue tenofovir, clinicians can expect renal function to recover more rapidly than it declined.

Keywords: HIV, highly active antiretroviral therapy, kidney glomerulus, proximal kidney tubules

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Introduction

Tenofovir disoproxil fumarate (tenofovir) co-formulated with emtricitabine is the preferred nucleoside reverse transcriptase inhibitor combination for patients with HIV infection when starting antiretroviral therapy [1]. Tenofovir

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*See Appendix.

is mainly eliminated by the kidneys and its use is associated with reduced renal function [2]. Regular monitoring of renal function is recommended for all patients on tenofovir [1].

While early reports suggest that renal function recovers completely when patients discontinue tenofovir [3,4], larger recent studies suggest that some patients do not fully recover. In one study, only 42% of 24 patients recovered their pre-tenofovir estimated glomerular filtration rate (eGFR) [5]; in another, 59% of 183 patients returned to normal levels of eGFR but the time taken to recover varied considerably, with a mean of 22 months and an interquartile range (IQR) of 13 to 50 months [6].

It is difficult to estimate the rate of decline in eGFR for patients on tenofovir and its subsequent recovery if tenofovir is discontinued. First, patients with lower eGFR are more likely to discontinue tenofovir [7]. Secondly, the rate of recovery may well be greater in those patients who had a faster decline in eGFR [5]. These two factors create the potential for time-dependent confounding, so that standard methods of analysis may lead to biased estimates [8].

In this study, we used marginal structural models to overcome the bias of standard methods. Using observational data from the Swiss HIV Cohort Study (SHCS), we estimated the rate of decline in eGFR for patients on tenofovir and the subsequent rate of recovery if tenofovir was then discontinued.

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 [9]. In our study, we included all patients starting their first antiretroviral therapy regimen after 1 January 2002, when routine measurement of serum creatinine measurements began in the SHCS. Patients had to start with tenofovir and either efavirenz (EFV) or the ritonavir-boosted protease inhibitor (PI/r) lopinavir (LPV/r), atazanavir (ATV/r) or darunavir (DRV/r), plus either emtricitabine or lamivudine. Patients had to then remain on tenofovir for at least 1 year – otherwise we could not expect any decline in eGFR nor subsequent recovery if the use of tenofovir then ceased – and have at least one calibrated serum creatinine measurement between 6 months and 1 year after starting therapy. We included in our analyses all measurements from the baseline at 1 year after starting therapy until the last recorded measurement to date or until patients re-started tenofovir having previously discontinued the drug, whichever came first. We calculated eGFR (in ml/min/1.73 m^2) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [10]; we used only calibrated measurements because different SHCS centres use different measurement techniques.

Statistical analyses

We estimated the difference in eGFR over time between patients discontinuing tenofovir and patients remaining on tenofovir using marginal structural models for repeated measures [8,11]. These models used inverse probability weights for confounder control: treatment weights to adjust for differences in patients discontinuing or remaining on tenofovir over time; censoring weights to adjust for differences between patients continuing to provide measurements over time and those lost to follow-up or re-starting tenofovir. Inverse probability weights were estimated by logistic regression using covariates likely to determine whether patients discontinued or re-started tenofovir or were lost to follow-up: gender, ethnicity, injecting drug use as the likely mode of transmission, age at baseline and initial antiretroviral regimen (EFV, LPV/r, ATV/r or DRV/r); and time-updated measurement of diabetes, hepatitis C virus coinfection, hypertension, body mass index, viral load, CD4 cell count and eGFR. We avoided extreme weights by truncating inverse probability weights at their 1st and 99th percentiles if below or above these values, respectively [12].

In our main analysis, we fitted a sequence of three models. In model 1, we used a cubic spline [13] to represent the decline in eGFR over time for patients remaining on tenofovir and a piecewise linear spline [14] to represent the difference in eGFR for those discontinuing tenofovir, with a change in slope at 6 months after discontinuation. In model 2, we replaced the cubic spline with a straight line and in model 3, we replaced both the cubic spline and piecewise linear spline with straight lines.

In all three models, we assumed that patients on different regimens might have different baseline values after 1 year on tenofovir but that the subsequent rate of decline and recovery before and after discontinuing tenofovir would be the same regardless of regimen. We did not have sufficient data to estimate differences in the rate of decline and recovery between therapies in a single model. Therefore, in two exploratory analyses, we re-fitted this sequence of three models first to only those patients starting tenofovir with EFV and secondly to only those patients starting tenofovir with either LPV/r or ATV/r (as these two drugs appear to have similar effects on eGFR [7,15] while little is known about the effect of DRV/r).

We used SAS version 9.2 (SAS Institute Inc., Cary, NC) for all analyses.

Results

Patient flow

As at May 2013, 1049 patients had taken tenofovir continuously for at least 1 year, with at least one calibrated serum creatinine measurement between 6 months and 1 year after starting therapy (and having started one of the four regimens of interest; Table 1). These 1049 patients were then followed for a median of 26 months (IQR 13, 49 months). During this time, they had a median of 7 (IQR 3, 12) creatinine measurements with a median time between measurements of 3.3 months (IQR 2.8, 5.6 months).

Of the 1049 patients, 888 (85%) had a creatinine measurement in the 6 months prior to starting therapy. Patients started all four regimens with a similar median eGFR but after 1 year on therapy, the median eGFR was slightly lower in those starting tenofovir with a PI/r (Table 1). From baseline at 1 year, 259 patients (25%) went on to discontinue tenofovir after an additional median time on tenofovir of 17 months (IQR 7, 34 months). Those starting therapy with LPV/r or ATV/r had a lower median eGFR when they discontinued tenofovir than those starting with EFV. Among the few patients (45; 4%) followed after discontinuing tenofovir for as long as they had been on tenofovir, eGFR returned to its pre-therapy median only in those patients who started tenofovir with EFV.

Estimates of eGFR decline and recovery

In model 1, the estimated difference in eGFR slope between patients discontinuing tenofovir and patients remaining on tenofovir (Table 2) was not much greater in the first 6 months off tenofovir [4.1 mL/min/1.73 m^2 per year; 95% confidence interval (CI) −1.0 to 9.3 mL/min/1.73 m^2 per year] than in the period beyond 6 months (3.0 mL/min/1.73 m^2 per year; 95% CI 1.8 to 4.3 mL/min/1.73 m^2 per year). This result suggests that the difference was only slightly nonlinear. These two estimates were not appreciably different when the flexible cubic spline representing the rate of decline in eGFR was replaced by a straight line (model 2). This result suggests that, after 1 year on tenofovir, further decline in eGFR was approximately linear. Finally, the assumption that recovery was also approximately linear (model 3) provided estimates of an approximate linear rate of both decline in eGFR on tenofovir (−1.1 mL/min/1.73 m^2 per year; 95% CI −1.5 to −0.8 mL/min/1.73 m^2 per year) and recovery of eGFR after discontinuing tenofovir (2.1 mL/min/1.73 m^2 per year; 95% CI 1.3 to 2.9 mL/min/1.73 m^2 per year).

Table 1 (a) Patient characteristics at 1 year after starting tenofovir (TDF) with either efavirenz (EFV) or the ritonavir-boosted protease inhibitor lopinavir (LPV/r), atazanavir (ATV/r) or darunavir (DRV/r), plus either emtricitabine or lamivudine; (b) patient flow before and after starting antiretroviral therapy and, at each point, the corresponding median estimated glomerular filtration rate (eGFR) and interquartile range (IQR)

Characteristics	EFV (*n* = 501)	LPV/r (*n* = 219)	ATV/r (*n* = 189)	DRV/r (*n* = 140)
(a)				
Age (years) (median)	41	42	40	41
Female gender (%)	16	25	23	10
Black ethnicity (%)	15	13	11	6
Injecting drug use as the likely mode of transmission (%)	5	10	13	3
Time since HIV diagnosis (months) (median)	23	15	32	14
Advanced infection (CDC group C) (%)	14	30	14	18
Hepatitis C virus coinfection (%)	10	16	21	6
Diabetes (%)	5	3	3	1
Hypertension (%)	23	27	22	26
HIV RNA (log_{10} copies/ml) (median)	1.3	1.6	1.5	1.3
CD4 count (cells/μL) (median)	421	412	428	465
Body mass index (kg/m^2) (median)	24	23	24	24
(b)				
Number of patients with eGFR measurements				
Prior to starting TDF	417	174	166	131
One year after starting TDF	501	219	189	140
Prior to stopping TDF	103	77	63	16
Remaining off TDF for as long as having received TDF	15	18	11	1
eGFR (mL/min/1.73 m^2) [median (IQR)]				
Prior to starting TDF	105 (93, 115)	106 (95, 115)	107 (95, 116)	107 (94, 118)
One year after starting TDF	104 (94, 115)	102 (87, 111)	100 (85, 110)	100 (89, 111)
Prior to stopping TDF	99 (83, 114)	94 (73, 109)	94 (76, 106)	103 (69, 112)
Remaining off TDF for as long as having received TDF	104 (71, 114)	95 (80, 110)	82 (73, 103)	84 (84, 84)

CDC, Centers for Disease Control and Prevention.

Table 2 Estimates of the decline and recovery in estimated glomerular filtration rate (eGFR) for patients starting tenofovir (TDF) with either efavirenz (EFV) or the ritonavir-boosted protease inhibitor lopinavir (LPV/r), atazanavir (ATV/r) or darunavir, plus either emtricitabine or lamivudine

	Model and rate parameters (mL/min/1.73 m^2 per year) (95% confidence interval)		
	All patients (n = 1032)*	Patients starting tenofovir with EFV (n = 495)*	Patients starting tenofovir with LPV/r or ATV/r (n = 398)*
Model 1			
Decline – cubic spline 5 knots	Not available†	Not available†	Not available†
Time off TDF – first 6 months	4.1 (–1.0 to 9.3)	4.5 (–3.8 to 12.8)	4.8 (–1.8 to 11.4)
Time off TDF – after 6 months	3.0 (1.8 to 4.3)	3.3 (0.4 to 6.2)	2.7 (1.2 to 4.2)
Model 2			
Linear rate of decline	–1.2 (–1.5 to –0.8)	–1.3 (–1.9 to –0.7)	–1.1 (–1.5 to –0.7)
Time off TDF – first 6 months	3.9 (–1.2 to 8.9)	4.5 (–3.7 to 12.6)	4.0 (–2.6 to 10.6)
Time off TDF – after 6 months	3.2 (1.8 to 4.4)	3.3 (0.4 to 6.2)	2.9 (1.3 to 4.5)
Model 3			
Linear rate of decline	–1.1 (–1.5 to –0.8)	–1.3 (–1.9 to –0.7)	–1.1 (–1.5 to –0.7)
Time off TDF – at any time	3.3 (2.4 to 4.2)	3.5 (1.5 to 5.5)	3.1 (2.0 to 4.2)
Linear rate of recovery‡	2.1 (1.3 to 2.9)	2.2 (0.3 to 4.2)	2.0 (1.0 to 3.0)

*The number of patients in each analysis is slightly lower than the corresponding number in Table 1 because a total of 17 patients had no further creatinine measurements after 1 year on tenofovir.
†No easily interpretable estimate is available for this model, because the rate of decline is represented by a flexible curve.
‡Found by summing the previous two parameters (with a confidence interval found from the parameter variance covariance matrix).

In model 1, patients starting tenofovir with DRV/r had similar eGFR at baseline to those starting tenofovir with EFV (estimated difference 0.0 mL/min/1.73 m^2; 95% CI –1.7 to 1.7 mL/min/1.73 m^2). There is some evidence that patients starting tenofovir with LPV/r or ATV/r had a lower eGFR at baseline than those starting tenofovir with EFV [with estimated differences of –0.7 mL/min/1.73 m^2 (95% CI –2.3 to 0.8 mL/min/1.73 m^2) and –1.4 mL/min/1.73 m^2 (95% CI –3.2 to 0.3 mL/min/1.73 m^2), respectively].

In the two exploratory analyses, estimates of the rate of decline in eGFR and its recovery after discontinuing tenofovir were similar when the three models were fitted to either only those patients starting tenofovir with EFV or only those patients starting tenofovir with either LPV/r or ATV/r (Table 2).

Discussion

It is important to understand how eGFR recovers when tenofovir is discontinued, because in the future patients on tenofovir may switch to new treatment combinations [16]. Our modelling of observational data suggests that, after 1 year on tenofovir, the approximate rate of further decline in eGFR is about 1 mL/min/1.73 m^2 per year and is about half the approximate rate of recovery in eGFR if patients then discontinue taking tenofovir. This implies that most patients should recover pre-therapy renal function by the time they have been off tenofovir for as long as they were on it. Our data suggest that this indeed happens, at least for patients starting tenofovir with EFV. For the 15 patients starting tenofovir with EFV and then remaining off tenofovir for as long as they were on it, the median difference between pre-therapy and post-recovery eGFR values was 0.1 (IQR –9.4, 2.7) mL/min/1.73 m^2.

For patients starting tenofovir with a PI/r, the picture is more complicated. In an earlier study, we found an initial decrease in eGFR when starting tenofovir with LPV/r or ATV/r rather than with EFV, but no further decrease beyond the first 6 months of therapy [15] and in this study, while patients starting tenofovir with LPV/r or ATV/r had lower eGFR at baseline (that is, after 1 year on tenofovir) than patients starting tenofovir with EFV, the two groups of patients had similar rates of decline in eGFR beyond 1 year and similar rates of recovery when tenofovir was discontinued.

However, patients starting tenofovir with a PI/r did not appear to recover their pre-therapy eGFR. For the 30 patients starting tenofovir with a PI/r and then remaining off tenofovir for as long as they were on it, the median difference between pre-therapy and post-recovery eGFR values was –7.9 (IQR –15.9, 3.6) mL/min/1.73 m^2. Of these 30 patients, 18 were still on a PI/r post-recovery. Ritonavir inhibits creatinine secretion [17] and the corresponding immediate but nonprogressive increase in serum creatinine leads to a one-off decrease in eGFR [18]. Hence patients on tenofovir with LPV/r or ATV/r might still recover their true pre-therapy glomerular filtration rate after discontinuing tenofovir without recovering their pre-therapy eGFR. Analyses using eGFR must be interpreted with caution [18,19]: LPV/r and ATV/r are thought to increase the risk of renal impairment [7] but their contribution could be exaggerated when eGFR is used to assess that risk.

Note that our estimated rate of decline in eGFR after 1 year is the same as the accepted 'normal' decline in glomerular filtration rate with age (1 mL/min/1.73 m^2 per year [20]). However, much of this 'normal' decline has been attributed to comorbidities that inevitably accompany ageing [21–23]. This makes it difficult to judge how much tenofovir has contributed to the rate of decline in renal function in these patients. That the decline in eGFR reversed when tenofovir was discontinued suggests that tenofovir was responsible, at least in part, for the decline.

This study has the same limitations as our earlier study [15]. In addition, we did not have sufficient data to estimate, in a single model, differences between regimens in the rate of decline in eGFR and its recovery if tenofovir is discontinued. This can be done using a marginal structural model but requires artificial censoring of patients when they change their baseline regimen [24,25] and this artificial censoring reduces the power of the analysis. The strengths of this study are the use of calibrated creatinine measurements and of statistical methods that minimize any bias attributable to time-dependent confounding.

When monitoring eGFR in patients starting tenofovir with either EFV, LPV/r or ATV/r, clinicians can expect renal function to recover more rapidly than it declined if patients discontinue tenofovir. On average, patients on a PI/r may not recover their pre-therapy eGFR after discontinuing tenofovir, but is not clear yet whether this has clinical consequences. While on average patients can be expected to recover their renal function after discontinuing tenofovir, not all patients will do so.

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Contributions to authorship: CF, EB, HF, PV, AC, MC, RW and MB were responsible for data collection in their respective hospitals; HB, JY and QW designed this study; QW and JY carried out the statistical analyses; JY and QW wrote the first draft of the manuscript; JY, QW and HB revised the manuscript; all authors reviewed, commented on, and approved the final version of the manuscript.

Appendix: Members of the Swiss HIV Cohort Study

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