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

J Young[1*], Q Wang[1], CA Fux[2], E Bernasconi[3], H Furrer[4], P Vernazza[5], A Calmy[6],

M Cavassini[7], R Weber[8], M Battegay[9], HC Bucher[1,9] and the Swiss HIV Cohort Study

[1] Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland

[2] Internal Medicine, Kantonsspital Aarau, Switzerland

[3] Regional Hospital of Lugano, Switzerland

[4] Department of Infectious Diseases, University Hospital Bern and University of Bern, Switzerland

[5] Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St Gallen, Switzerland

[6] Division of Infectious Diseases, University Hospital Geneva, Switzerland

[7] Division of Infectious Diseases, University Hospital Lausanne, Switzerland

[8] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Switzerland

[9] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Switzerland

[*]Corresponding author: Jim Young

Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, CH-4031 Basel, Switzerland

Phone +41 61 265 3100

Fax: +41 61 265 3109

Email: james.young@usb.ch

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Abstract

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 one year after starting a first antiretroviral therapy with tenofovir and either efavirenz or the ritonavir boosted protease inhibitors lopinavir, atazanavir or darunavir. We estimated the difference in eGFR slope between those who discontinued tenofovir after one year and those who remained on tenofovir.

Results: 1049 patients on tenofovir for at least one year were then followed for a median of 26 months, during which time 259 (25%) patients discontinued tenofovir. After a 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 1.70) mL/min per 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 per 1.73 m^2 per year and its recovery after discontinuing tenofovir was 2.1 (95% CI 1.3 to 2.9) mL/min per 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.

Introduction

Tenofovir disoproxil fumarate (tenofovir) co-formulated with emtricitabine is the preferred reverse transcriptase inhibitor combination for patients with HIV when starting antiretroviral therapy [1]. Tenofovir 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]. Second 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 use marginal structural models to overcome the bias of standard methods. Using observational data from the Swiss HIV Cohort Study (SHCS), we estimate the rate of decline in eGFR for patients on tenofovir and the subsequent rate of recovery if tenofovir is then discontinued.

Methods

Patients

The SHCS is a multi-centre, 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 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

inhibitors (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 one 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 one year after starting therapy. We included in our analyses all measurements from the baseline at one 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 per 1.73m2) 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, injection 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 co-infection, 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 six 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 patients on different regimens might have different baseline values after one 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 second 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, USA) for all analyses.

Results

Patient flow

As at May 2013, 1049 patients had taken tenofovir continuously for at least one year, with at least one calibrated serum creatinine measurement between 6 months and one 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). 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).

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 one year on therapy, the median eGFR was slightly lower in those starting tenofovir with a PI/r (Table 1). From baseline at one year, 259 (25%) patients went on to discontinue tenofovir after an additional median time on tenofovir of 17 months (IQR 7, 34). 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 that 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 six months off

tenofovir (4.1, 95% confidence interval (CI) -1.0 to 9.3 [mL/min per 1.73 m^2 per year]) than in the period beyond six months (3.0, 95% CI 1.8 to 4.3). This result suggests the difference was only slightly non-linear. These two estimates were not appreciable 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 one year on tenofovir, further decline in eGFR was approximately linear. Finally, assuming recovery was also approximately linear (Model 3) provided estimates of an approximate linear rate of both decline in eGFR on tenofovir (-1.1, 95% CI -1.5 to -0.8) and its recovery after discontinuing tenofovir (2.1, 95% CI 1.3 to 2.9).

In Model 1, patients starting tenofovir with DRV/r had similar eGFR at baseline to those starting tenofovir with EFV (estimated difference 0.0, 95% CI -1.7 to 1.7 [mL/min per 1.73 m^2]). There is some evidence patients starting tenofovir with LPV/r or ATV/r had a lower eGFR at baseline than those starting tenofovir with EFV (with estimated differences -0.7, 95% CI -2.3 to 0.8, and -1.4, 95% CI -3.2 to 0.3, 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 fit 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 one year on tenofovir, the approximate rate of further decline in eGFR is about 1 mL/min per 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 suggests 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 was 0.1 (IQR -9.4, 2.7) mL/min per 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 six 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 one year on tenofovir) than patients starting tenofovir with EFV, both groups of patients had a similar rate of decline in eGFR beyond one year and a similar rate 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 was -7.9 (IQR -15.9, 3.6) mL/min per 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 non-progressive 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 one year is the same as the accepted "normal" decline in glomerular filtration rate with age (1 mL/min per 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 minimise any bias due 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.

Acknowledgements

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Table 1: A: Patient characteristics at one year after starting tenofovir (TDF) with either efavirenz (EFV) or the ritonavir-boosted protease inhibitors 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).

	EFV	LPV/r	ATV/r	DRV/r
A: Characteristics	n=501	n=219	n=189	n=140
Median age, years	41	42	40	41
Female gender, %	16	25	23	10
Black ethnicity, %	15	13	11	6
Intravenous drug use as the likely mode of transmission, %	5	10	13	3
Median time since HIV diagnosis, months	23	15	32	14
Advance infection (CDC Group C), %	14	30	14	18
Hepatitis C co-infection, %	10	16	21	6
Diabetes, %	5	3	3	1
Hypertension, %	23	27	22	26
Median HIV RNA, $\log_{10}$ copies/ml	1.3	1.6	1.5	1.3
Median CD4 cell count, cells/mm^3	421	412	428	465
Median body mass index, kg/m^2	24	23	24	24
B: Patient flow				
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
Median eGFR, mL/min per 1.73 m^2 (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)

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 inhibitors lopinavir (LPV/r), atazanavir (ATV/r) or darunavir, plus either emtricitabine or lamivudine.

Model and rate parameters, mL/min per 1.73 m^2 per year (95% confidence interval)	All patients n=1032 [1]	Patients starting tenofovir with EFV n=495 [1]	Patients starting tenofovir with LPV/r or ATV/r n=398 [1]
Model 1			
Decline – cubic spline 5 knots	Not available [2]	Not available [2]	Not available [2]
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 [3]	2.1 (1.3 to 2.9)	2.2 (0.3 to 4.2)	2.0 (1.0 to 3.0)

[1] 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 one year on tenofovir.

[2] No easily interpretable estimate is available for this model, because the rate of decline is represented by a flexible curve.

[3] Found by summing the previous two parameters (with a confidence interval found from the parameter variance covariance matrix).