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Renal impairment in a large-scale HIV pre-exposure prophylaxis implementation cohort

Running title: Renal impairment in PrEP implementation

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Abstract

Background: HIV pre-exposure prophylaxis (PrEP) with fixed-dose tenofovir disoproxil fumarate (TDF) and emtricitabine has been associated with low rates of renal impairment in clinical trials. Large-scale PrEP implementation may result in higher rates, as the prevalence of associated risk factors may be higher than in trial populations.

Methods: A post-hoc analysis of EPIC-NSW, a large Australian multi-centre PrEP implementation trial for patients at high-risk of HIV infection. Participants were eligible for inclusion if they commenced PrEP between 1 March 2016 and of 30 April 2018, and had renal function assessed at baseline and at least once more before the censor date. The primary outcome was new onset renal impairment, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2.

Results: 6808 participants were eligible for inclusion. Almost all were male (99%), with a median age of 35 years (IQR: 28 to 44). Approximately one-quarter (26%) had a baseline eGFR <90 mL/min/1.73m^2. Over a median follow-up period of 1.2 years (IQR 0.6 to 1.7), the rate of renal impairment was 5.8 episodes per 1000 person years (95%CI: 4.0 to 7.8). In multivariable Cox regression, there was higher risk of renal impairment in participants aged ≥50 years (HR 14.7, 95%CI: 5.0 to 43.3, p<0.001) and those with an eGFR <90 mL/min/1.73m^2 (HR 28.9, 95%CI: 6.9 to 121.9) at baseline.

Conclusion: In a large-scale implementation study, TDF-containing PrEP was associated with a low risk of renal impairment overall, while older patients and those with pre-existing renal dysfunction were at substantially increased risk.

MeSH Terms

HIV, pre-exposure prophylaxis, tenofovir, kidney disease, risk factors

Abbreviations

eGFR – estimated glomerular filtration rate

PrEP – pre-exposure prophylaxis

TAF – tenofovir alafenamide

TDF – tenofovir disoproxil fumarate

Introduction

Pre-exposure prophylaxis (PrEP) with fixed-dose tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has been shown to be efficacious in preventing HIV infection in clinical trials and, more recently, to be effective at a population level in the large-scale EPIC-NSW implementation study.[1-4] While TDF is generally well tolerated, it is a potential nephrotoxin.

The use of TDF for PrEP is associated with a small and generally non-progressive reduction in estimated glomerular filtration rate (eGFR), with a minority of patients developing clinically significant renal impairment.[5-7] Earlier placebo-controlled trials and subsequent implementation studies have differed, however, in the reported incidence of this TDF-associated renal impairment. A meta-analysis of the former found the risk of creatinine elevations no greater in PrEP patients than those receiving placebo.[8] In contrast, implementation studies have generally reported between two to ten-fold higher rates of renal impairment than in randomised trials, depending on how renal impairment was defined.[5, 7, 9-11]

These differences in the risk of renal impairment may be due to the placebo-controlled studies, and their open label extensions, having included fewer older patients and/or patients with pre-existing renal dysfunction as compared to later implementation studies, two patient groups being known to be at increased risk of TDF-induced renal impairment.[7, 9-11] The implementation studies have tended to be smaller than the earlier placebo-controlled trials, however.[7, 8, 10] The incidence of renal impairment in "real world" PrEP populations therefore may not be well characterised.

Despite the potential for nephrotoxicity, daily dosing with TDF-containing PrEP is currently recommended by major international societies for HIV prevention and uptake of TDF-containing PrEP is increasing.[12-15] Alternatives to daily dosing with TDF-containing PrEP exist, including event driven PrEP, which offers reduced TDF exposure, and the novel prodrug tenofovir alafenamide (TAF), with less renal toxicity.[16]

With the continued uptake of PrEP and the emergence of alternatives to daily TDF dosing, a more precise estimation of the risk of renal impairment in a "real world" population would aid in clinical decision making. Here we report the incidence and predictors of new onset renal impairment in patients taking once daily PrEP for HIV prevention in EPIC-NSW, a prospective large-scale PrEP implementation study in Australia.

Methods

This study was a post-hoc analysis of data from the EPIC-NSW, a large multi-centre prospective PrEP implementation trial in Australia. In brief, EPIC-NSW evaluated the use of once-daily, fixed-dose TDF/FTC (300/200 mg) for HIV prevention in individuals at high-risk of HIV infection, as defined by behavioural eligibility criteria and/or recent diagnosis of particular sexually transmitted infections. Those with a baseline eGFR < 60 mL/min/1.73m^2 were excluded. Renal function was measured at baseline, three months after commencing PrEP and then every six months thereafter, with more frequent monitoring at the discretion of each participating clinic. The full protocol of the trial has been published previously.[17]

Study population

In this analysis, data were used from participants enrolled in the EPIC-NSW trial from 1 March 2016 to 30 April 2018 inclusive. Participants were eligible for inclusion if they had PrEP dispensed at least once, a baseline eGFR measurement (closest measure to PrEP commencement, between 365 days prior to treatment and 30 days after commencement) and at least one subsequent eGFR measure. A subset of participants from a single clinic were excluded, as their data had been previously reported.[11]

Data source

Data were extracted from 31 clinics in the Australian state of New South Wales and the Australian Capital Territory. Data were collected as part of routine care and then extracted and transferred regularly to the Kirby Institute via GRHANITE data extraction software.[18] Where clinics did not have systems compatible with this data extraction software, trial data was entered by clinics into an online reporting tool. This data extraction collected only eGFR values, calculated using the CKD-EPI equation, but not the original serum creatinine measurements.

Data from eligible participants were analyzed from the date of first PrEP dispensing until detection of renal impairment or the study censor date of April 30, 2018. Although the primary study continued after this date, adherence data were no longer available as patients began to obtain PrEP via community pharmacies after the formulation became eligible for government subsidy. Participants were censored earlier if they withdrew from the study or were considered lost to follow-up, defined as not having eGFR test data available for greater than 365 days, with censoring effective from 182 days after the last available measure. This method of censoring assumed a uniform distribution of loss to follow-up over the interval.

Outcomes and predictors

New onset renal impairment was defined as an eGFR < 60 mL/min/1.73m^2. To account for spurious measures, this needed to be confirmed by the average of that measurement and next also being < 60 mL/min/1.73m^2. In contrast, pre-existing renal dysfunction refers to a baseline eGFR < 90 mL/min/1.73m^2. A sensitivity analysis was conducted in which renal impairment also included instances of eGFR < 60 mL/min/1.73m^2 where patients were then lost to follow-up or censored (Appendix A, http://links.lww.com/QAD/C250). A further subgroup analysis of patients with a baseline eGFR < 90 mL/min/1.73m^2 was performed, where renal impairment was alternatively defined as a confirmed eGFR decline to < 60 mL/min/1.73m^2 or a decrease of > 25% from baseline.

Potential risk factors for renal impairment were explored in a secondary analysis. These factors included age group (<40, 40-49, ≥50 years), gender, baseline eGFR (≤90, >90 mL/min/1.73m^2), geographical remoteness of patient (major city, inner regional, outer regional/remote) and hepatitis C serological status. Quarterly medication possession ratio was calculated as the number of PrEP pills a participant was dispensed, divided by the time between dispensing visits (or until censor date), assuming once-daily dosing, with a maximum value of 1. We report time updated MPR as a three-level categorical variable:

"low" (lower quartile of MPR values), "medium" (above lower quartile and less than perfect adherence), and "high" (perfect adherence).

Statistical analysis

Rates of renal impairment, by risk factor, were calculated as cases per 1000 person-years. Cumulative probability of renal impairment over time was estimated using the Kaplan-Meier method, to a maximum of two years, with difference between both rates and survivor curves measured using log rank tests. Bivariate Cox proportional hazards models, stratified by study clinic, were used to assess determinants of time to failure for each risk factor listed above. Variables with a p-value < 0.1 in bivariate analysis were included in a multivariable model. All analyses were conducted using Stata version 15.1 (StataCorp, USA) with a p-value < 0.05 considered statistically significant.

Results

Between March 2016 and April 2018, there were 9586 participants in the EPIC-NSW trial who had been dispensed PrEP and had baseline renal function data available. Patients from a single clinic (N=572) were excluded from further analysis, as their data had been described previously.[11] A further 2206 participants were excluded for not having both baseline renal function data and at least one follow-up measure within the study period. This was largely due to recruitment of these participants later in the study period, with insufficient time for two renal function tests in the study. Data from 6808 participants were eligible for inclusion in this analysis of renal function, with 7874 person-years of follow-up and a median follow-up time of 1.2 years (IQR: 0.6 to 1.7).

Baseline characteristics of study participants are detailed in Table 1. Almost all were male (99%) and resided in major cities (95%). Median age was 35 years (IQR 28 to 44), with 14% of the cohort being 50 years of age or older at enrolment. At baseline, nearly one-third of the cohort had an eGFR < 90 mL/min/1.73m^2 (27%) and nine percent had previous exposure to PrEP. Use of methamphetamine within the last three months was reported by one-fifth of participants (19%) and positive hepatitis C virus serology was noted in one percent.

There were 46 instances of new onset renal impairment over the study period, corresponding to a rate of 5.8 instances per 1000 person-years (95%CI: 4.4 to 7.8). Rates of renal impairment are shown by participant subgroup in Table 2. Confirmatory testing occurred in a median of 65 days (IQR: 28 to 91) after renal impairment was first detected. The cumulative risk of renal impairment increased in a roughly linear manner (Figure 1) and, at two years of follow-up, was 1.34% (95%CI: 0.95 to 1.89). Participants that were ≥ 50 years of age at enrolment, however, had more than a four-fold higher cumulative risk of developing renal impairment at two years than younger participants (6.46%, 95%CI: 4.4 to 9.4, p<0.001). Similar trends were seen in the sensitivity analysis where renal impairment also included patients with a single eGFR measure < 60 mL/min/1.73m^2 and were either lost to follow-up or censored (Appendix A, http://links.lww.com/QAD/C250).

Adherence to PrEP, measured by medication possession ratio, was high. Patients were dispensed PrEP at three-monthly study visits. Of the intervals between these visits, 89.2% had a medication possession ratio associated with a protective level of TDF, equivalent to

four tablets per week.[19] There was no PrEP coverage, however, in 10.3% of these intervals due to missed dispensing visits. Delayed study visits resulted in 0.5% of intervals having a medication possession ratio that was less than protective. The three MPR levels used to assess the association of different PrEP adherence levels with renal impairment were < 0.11 (low), 0.11-0.99 (medium) and >0.99 (high).

In bivariate Cox proportional hazards regressions (Table 2), baseline eGFR < 90 mL/min/1.73m^2 (p<0.001), age 40 – 49 years (p=0.002) and age ≥ 50 years (p<0.001) were associated with a higher risk of renal impairment. No such association was found for recent methamphetamine use (p=0.403), positive hepatitis C serology (p=0.553) or previous PrEP use (p=0.654). As compared to low MPR, there was no increased risk associated with either medium (p=0.180) or high (p=0.077) MPR.

In a multivariable model, there was a substantially higher risk of renal impairment in participants aged ≥ 50 years (HR 14.7, 95%CI: 5.0 to 43.3, p<0.001) and those with a baseline eGFR < 90 mL/min/1.73m^2 (HR 28.9, 95%CI: 6.9 to 121.9, p<0.001).

A subgroup analysis was performed on participants with baseline eGFR < 90 mL/min/1.73m^2, where renal impairment was a composite outcome of confirmed eGFR < 60 mL/min/1.73m^2 or a decrease in eGFR of > 25% from baseline (Figure 2). With this definition, there were 22.0 episodes per 1000 patient years (95%CI: 16.6 to 29.1) of new renal impairment. This equated to a cumulative risk of 5.6% (95%CI 3.3 to 6.3) at two years of follow-up.

Discussion

In this retrospective post-hoc analysis of 6,808 EPIC-NSW study participants, there were 46 instances of new onset renal impairment during 7,874 person-years of follow-up, corresponding to a rate of 5.6 instances per 1,000 person-years. The risk of renal impairment was substantially higher in patients with pre-existing renal dysfunction and older patients, particularly those aged 50 or older.

The proportion of participants who developed renal impairment in our study (0.7%) was five-fold greater than the 0.1% reported in both the iPrEX open label extension and the Partners PrEP Study.[9, 20] This was despite longer median follow-up times in both these studies; one-and-a-half and three years, respectively. Given that 15 participants in our study were found to have an eGFR <60 mL/min/1.73m^2 and were then lost to follow-up or censored, our reported rate of renal impairment may be an underestimate. This underestimate is likely to be small, however, as spurious eGFR results are common. In IPERGAY, fewer than a quarter of abnormal eGFR measures were confirmed on retesting and fewer than a fifth were confirmed in the main iPrEx trial. [6, 21]

Compared to those < 40 years of age, participants aged 40 - 49 or ≥ 50 years at study enrolment had a 4-fold and 14-fold high risk of developing renal impairment during the study period respectively. A baseline eGFR < 90 mL/min/1.73m^2 was independently associated with 29-fold increased risk of renal impairment. Age and pre-existing renal dysfunction have been consistently identified as risk factors for renal impairment across PrEP studies with the

relative risk/odds ratios ranging from less than ten-fold increases in implementation studies from the United States to over 30-fold in the iPrEx open label extension.[7, 9-11]

The higher rate of renal impairment in our study, as compared to previous PrEP studies, is likely explained by a greater proportion of participants with these risk factors. In the iPrEx open label extension, for example, only 8.6% of participants were aged 50 or older and 8.5% had pre-existing renal impairment. This compares to 14% aged over 50 and 29% with pre-existing renal impairment in our study. Higher prevalence of these risk factors appears to be a common feature of PrEP implementation studies,[7, 10, 22] suggesting that the "real world" incidence of TDF-induced renal impairment would be greater than that reported in earlier randomised controlled trials and their open label extensions.[5, 6, 9, 21] Our findings support current recommendations that patients with these risk factors should receive more frequent monitoring of their renal function and that clinicians could consider alternatives to daily dosing of TDF-containing PrEP.[12, 13]

The definition of confirmed renal impairment in this study was chosen to accommodate variations in re-testing practice between study sites. Australian guidelines now recommend confirmatory testing of abnormal eGFR values within seven days,[12] but no such recommendation existed at the time of the study. The median interval for re-testing of renal function of 84 days suggests that participants were generally not being recalled for repeat testing ahead of planned three-monthly study visits.[17] While TDF-induced renal impairment was shown to be largely reversible in the Partners PrEP study, their protocol required abnormal eGFR values be reassessed within seven days and those with confirmed renal impairment to have TDF discontinued immediately.[23] The extent to which ongoing TDF exposure in PrEP patients with new renal impairment would limit reversibility is, as yet, unclear. Caution is warranted however, as both duration of TDF exposure and the extent of the decline in eGFR have been associated with poorer reversibility of TDF-induced renal impairment in people living with HIV.[24]

There was a trend towards high MRP being associated with greater risk of renal impairment, although this did not reach statistical significance. Using hair samples to measure PrEP adherence, both the iPrEx open label extension and US PrEP Demonstration studies reported a dose response relationship between TDF use and reductions in creatinine clearance.[7, 9] However, these studies similarly did not find that more regular PrEP use was associated with a higher incidence of new onset renal impairment.

Intermittent dosing of TDF-containing PrEP has been shown to be similarly efficacious to daily regimens and has the theoretical benefit of reduced renal toxicity from lower TDF exposure. this benefit remains to be convincingly demonstrated by trial data, however.[1] In IPERAGY, while the risk of serious adverse renal events was similar between the intermittent dosing and placebo groups, those on PrEP were sill at significantly increased risk of creatinine elevations.[21] Head-to-head data comparing daily-dosing and intermittent PrEP regimens are limited,[25] and further study, particularly in relation to high-risk groups, may be warranted.

TAF, a novel prodrug of the active metabolite tenofovir, may represent a safer alternative for patients at risk of TDF-induced nephrotoxicity. TAF appears to be associated with lower rates

of renal impairment among people living with HIV.[26] DISCOVER, the first trial comparing TDF to TAF for PrEP is ongoing, with early results suggesting lower rates of renal and bone toxicity.[16] The lower cost of generic TDF is likely to justify its continued use in lower risk groups.

Markers of renal proximal tubular dysfunction, including proteinuria and urinary phosphate excretion, were not measured in this study. TDF exposure is associated with proteinuria among people living with HIV,[26] however, the association is less robust when TDF is used for PrEP. In Partners PrEP and iPrEx, two large placebo-controlled studies, TDF exposure was associated with proteinuria in the former, but not the latter trial.[5, 27] Although, tubular proteinuria was noted in the iPrEx open label extension study.[27] New onset proteinuria during PrEP, however, does not appear to increase the risk of new onset renal impairment.[5, 11]

The main limitation of this analysis was its median follow-up time of just over one year, we cannot exclude the possibility of increasing rates of renal impairment with cumulative TDF exposure. However, the Bangkok Tenofovir Study, which followed PrEP patients out to five years, did not report such an increase.[28] As in the earlier PrEP studies though, the study population in the Bangkok study was young, with nearly half of participants being under the age of 20 years.[29] Whether the risk of renal impairment increases with chronic TDF exposure in a "real world" PrEP population therefore remains to be explored.

The collection of pre-calculated eGFR values from the participating clinics meant that higher eGFR values were reported as ">90" mL/min/1.73m^2, precluding analysis of changes in eGFR, as reported in other PrEP studies [5]. In our subgroup analysis of patients with a baseline eGFR < 90 mL/min/1.73m^2, however, the addition of a decline in eGFR > 25% in the definition of new renal impairment only increased the overserved rate from 17.5 to 22.0 instances per 1000 patient years. This suggests that the collection of pre-calculated eGFR values did not substantially affect our estimates of renal impairment.

We did not collect data on participant ethnicity and thus are unable to comment on whether some groups are at increased risk TDF-containing PrEP, although this has not been demonstrated in other PrEP implementation studies.[7, 10] We did not have access to the indigenous status of patients. Indigenous Australians have been shown to be at substantially higher risk of renal disease[30] and higher risk of HIV-infection, as compared to non-indigenous Australians.[31] The safety of TDF-containing PrEP in this population is therefore an important area for future study.

Conclusion

In EPIC-NSW, a large-scale PrEP implementation study, the incidence of renal impairment was low, but substantially higher than reported in previous clinical trials. New onset renal impairment in our study was largely confined to patients with pre-existing renal dysfunction and/or those aged 50 years or older, suggesting that daily dosing of TDF-containing PrEP in young, healthy patients is safe from a renal perspective. For those with risk factors, more frequent clinical monitoring may be warranted.

Appendix B, http://links.lww.com/QAD/C251

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Figure Legends

Figure 1. Kaplan-Meier estimates of cumulative probability of new-onset renal impairment (confirmed eGFR < 60 mL/min/1.73m^2) in patients by age group. eGFR – estimated glomerular filtration rate, PrEP – pre-exposure prophylaxis

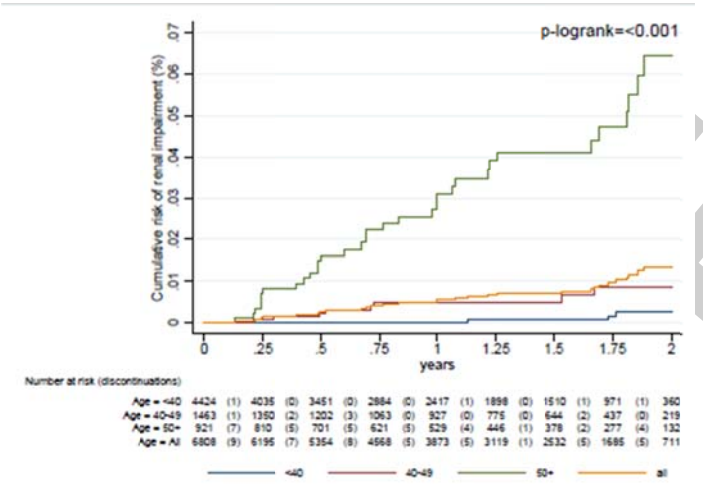

Figure 2. Kaplan-Meier estimate of cumulative probability of new onset renal impairment (confirmed eGFR < 60 mL/min/1.73m^2 or >25% decrease in eGFR from baseline) in patients by age group. Shaded areas represent 95%CI. eGFR – estimated glomerular filtration rate, PrEP – pre-exposure prophylaxis

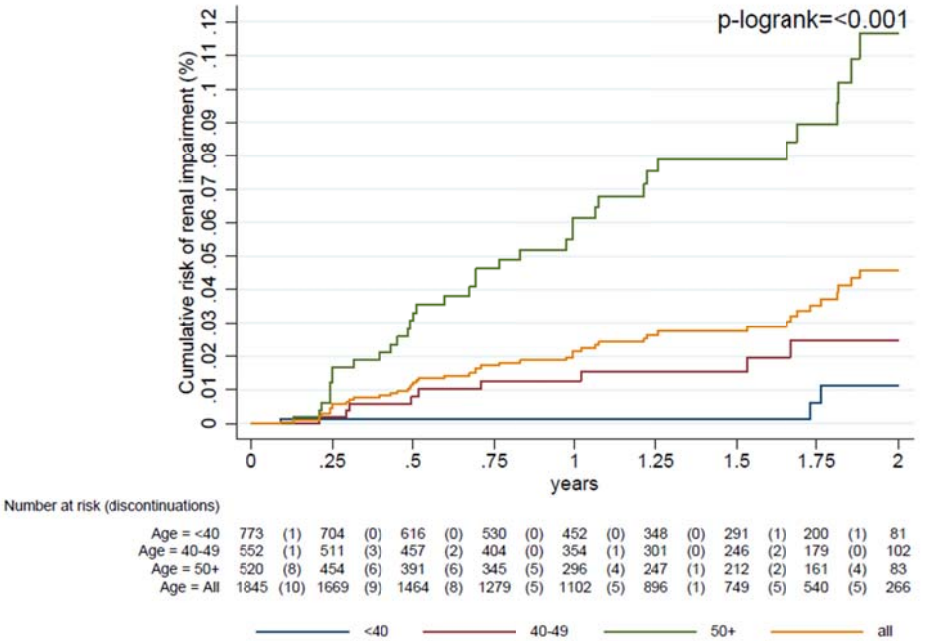

Table 1. Baseline characteristics (n=6808)

Characteristic	Category	n (%)
Gender		
	Male	6762 (99)
	Female	5 (0)
	Other/Missing	69 (1)
Age group (years)		
	< 40	4424 (65)
	40 – 49	1463 (21)
	50 – 59	921 (14)
Area of residence		
	Major city	6454 (95)
	Inner regional	235 (3)
	Outer regional or remote	33 (0)
	Missing	86 (1)
Baseline eGFR (mL/min/1.73m^2)		
	> 90	4963 (73)
	≤ 90	1845 (27)
Methamphetamine use*		
	No	5519 (81)
	Yes	1289 (19)
Hepatitis C antibody		
	No	6728 (99)
	Yes	80 (1)
Previous PrEP use**		
	No	6237 (91)
	Yes	525 (9)

eGFR – estimated glomerular filtration rate, PrEP – pre-exposure prophylaxis * within three months of PrEP commencement, **within six months of PrEP commencement

Table 2. Event rates and Cox proportional hazards regression by potential risk factors for renal impairment

		Rate of renal impairment /1000 person years (95%CI)	p-value (logrank)	Bivariate HR (95%CI)	p-value	Bivariate pwald	Multivariate HR (95%CI)	p-value	Multivariate pwald
Age group (years)									
	< 40	0.8 (0.3 to 2.2)	<0.001	1 (ref)	-	<0.001	1 (ref)	-	<0.001
	40 – 49	4.9 (2.5 to 9.4)		6.7 (2.1 to 22.1)	0.002		3.5 (1.1 to 11.9)	0.041	
	≥ 50	30.2 (21.5 to 42.5)		43.8 (15.2 to 124.4)	< 0.001		14.7 (5.0 to 43.3)	< 0.001	
Baseline eGFR (mL/min/1.73m^2)									
	> 90	0.4 (0.1 to 1.4)	<0.001	1 (ref)	-		1 (ref)	-	
	≤ 90	19.7 (14.7 to 26.5)		64.0 (15.4 to 265.9)	< 0.001		28.9 (6.9 to 121.9)	< 0.001	
Methamphetamine use*									
	No	6.2 (4.5 to 8.5)	0.376	1 (ref)	-				
	Yes	4.6 (2.3 to 9.2)		0.7 (0.3 to 1.6)	0.403				
Hepatitis C antibody									
	No	5.8 (4.3 to 7.7)	0.553	1 (ref)	-				
	Yes	11.5 (1.6 to 81.6)		2.0 (0.3 to 14.3)	0.508				
MPR level									
	Low	3.9 (2.1 to 7.6)	0.252	1 (ref)	-	0.781			
	Medium	7.0 (3.3 to 14.6)		2.0 (0.7 to 5.3)	0.180				
	High	6.5 (4.6 to 9.3)		2.0 (0.9 to 4.3)	0.077				
Previous PrEP use**									
	No	5.9 (4.4 to 8.0)	0.654	1 (ref)	-				
	Yes	5.2 (1.9 to 13.7)		0.7 (0.2 to 2.4)	0.630				

* within three months of PrEP commencement, **within six months of PrEP commencement, MRP levels corresponded to a quarterly MPR of < 0.11 (low), 0.11-0.99 (medium) and >0.99 (high), eGFR – estimated glomerular filtration rate, MPR – medication possession ratio, PrEP – pre-exposure prophylaxis