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Frequency of monitoring kidney function in HIV-uninfected persons using daily oral tenofovir disoproxil fumarate pre-exposure prophylaxis

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Abstract

Background—Wide-scale implementation of oral tenofovir-based pre-exposure prophylaxis (PrEP) for HIV prevention is now policy in many settings. However, the optimal frequency for monitoring kidney function remains uncertain. We investigated the impact of 6-monthly compared to 3-monthly creatinine clearance (CrCl) monitoring on the identification of moderate kidney dysfunction, defined as CrCl <60 mL/min.

Methods—Data were from two prospective daily oral PrEP studies in Kenya and Uganda: the Partners PrEP Study, a randomized safety and efficacy trial of PrEP that conducted 3-monthly CrCl monitoring (n=4404) and the Partners Demonstration Project (n=954), an open-label delivery study of PrEP that used 6-monthly monitoring. CrCl ≥60 mL/min was required for enrollment in both studies. Abnormal results were followed with confirmatory testing within approximately 1 week. Follow-up was for up to 24 months.

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Results—Of 5358 participants included in the analysis, 87% were <45 years, a third were female, and 21% had a baseline CrCl between 60–90 mL/min. Confirmed CrCl <60 mL/min events were rare, occurring in 52 individuals (<1%) in 24-months. The 12-month cumulative proportion of persons with CrCl <60 mL/min was 0.2% with 3-monthly screening and 0.5% with 6-monthly screening.. Older age (>45 years), lower weight (<55 kg), and baseline CrCl between 60–90 mL/min were independently associated with CrCl decline <60 mL/min during follow up.

Conclusions—In these two PrEP studies, with a generally young participants, the occurrence and pattern of clinically relevant decline in CrCl were not qualitatively different based on 3- or 6-monthly CrCl monitoring schedule. These data suggest that for most persons receiving PrEP for up to 24 months, less frequent CrCl monitoring would be safe and reduce required expenditures for.

Introduction

Daily oral tenofovir disoproxil fumarate (TDF)-based pre-exposure prophylaxis (PrEP) is recommended as an HIV prevention strategy for at-risk persons globally. Preventative strategies in general must be safe, as they are provided to otherwise healthy persons to prevent a condition that they may or may not otherwise acquire. In clinical trials, TDF-based PrEP was associated with small non-progressive declines in estimated glomerular filtration rate (eGFR)[1–3], a commonly used measure of kidney function, but severe kidney dysfunction was very rare (<2%)[3–5].

In clinical trials of PrEP efficacy, kidney function, as estimated by creatinine clearance, was assessed every 3 months; follow-on PrEP demonstration projects, designed to include procedures that were close to “real world” settings, have used a variety of monitoring schedules, including both less and more frequently than the trials[6–14]. Currently, the U.S. Centers for Disease Control and Prevention recommends kidney monitoring every 6-months while on PrEP, and the World Health Organization recommends quarterly monitoring for the first 12 months of PrEP use and then annually thereafter; neither suggests differential monitoring based on specific risk factors. Studies have not formally investigated the optimal timing of kidney function monitoring while on PrEP or the potential for less frequent monitoring for some PrEP users.

As PrEP is delivered more widely, especially in resource-limited settings, it is important to define the optimal frequency of kidney safety monitoring that balances the clinical need to identify kidney dysfunction against the costs, complexity, and availability of laboratory testing. Using data from two prospective PrEP studies in East Africa which enrolled a generally young healthy population, we investigated whether 6-monthly kidney function monitoring could be as safe as 3-monthly monitoring.

Methods

Population

Data were from two large prospective PrEP studies, the Partners PrEP Study and the follow-on Partners Demonstration Project. Details of study design, recruitment, and primary outcomes of the two studies are reported elsewhere[7,8]. Briefly, the Partners PrEP Study was

a randomized clinical trial of the efficacy and safety of daily oral TDF and emtricitabine-TDF PrEP for HIV prevention among HIV-uninfected members of African heterosexual HIV serodiscordant couples conducted between 2008 and 2012 at nine clinical sites in Kenya and Uganda (Clinicaltrials.gov number NCT00557245)[7]. Monitoring of kidney function was conducted every 3 months. The follow on study, Partners Demonstration Project, was an open-label, delivery study of integrated PrEP for HIV-uninfected partners and antiretroviral therapy (ART) for the HIV-infected partners among high-risk HIV serodiscordant African couples conducted in 4 clinical sites in Kenya and Uganda (Clinicaltrials.gov number NCT02775929)[8]. In this study, which was designed to demonstrate a scalable public health delivery model for PrEP, kidney function monitoring was routinely conducted every 6 months. In both studies, abnormal results were followed with confirmatory testing within approximately 1 week and PrEP was withheld if clinically indicated.

For both studies, eligible HIV-uninfected participants at entry were ≥18 years of age, did not have active hepatitis B infection, were not pregnant or breastfeeding, had Cockcroft-Gault calculated creatinine clearance of ≥60 mL/min, were not receiving ongoing therapy with agents with known significant nephrotoxic potential, and did not have diabetes requiring hypoglycemic medication or active and clinically significant cardiac disease. In both studies, PrEP adherence was very high (>80 %)[7,8]. Protocols for both studies were approved by the University of Washington Human Subjects Division and by ethics review committees at each of the participating study sites. All participants provided written informed consent, and study progress for each study was reviewed by independent data monitoring committees.

Criteria for permanent study drug discontinuation

Permanent study drug discontinuation occurred under the following circumstances: (1) at completion of scheduled follow-up on study medication, (2) in participants who seroconverted to HIV infection, (3) in participants who experienced a confirmed grade 2 or higher serum creatinine abnormality (a Cockcroft– Gault calculated creatinine clearance, 50 mL/min). For participants with a recorded graded creatinine-related drug adverse event, serum creatinine was monitored weekly until the abnormality resolved or stabilized.

Laboratory testing—For both study cohorts, kidney function monitoring consisted of serum creatinine testing and calculation of creatinine clearance using the Cockoft-Gault equation with ideal body weight, at baseline and during follow-up. Serum creatinine was measured by local site laboratories which participated in regular proficiency testing for quality control and quality assurance prior to and during collection of biological specimens.

Analysis—The current analysis included persons who initiated PrEP and had at least one post-enrollment serum creatinine measurement. The primary outcome was the frequency of decline in calculated creatinine clearance to a level <60 mL/min; a decline of this magnitude is a frequently used measure for kidney dysfunction and is the recommended threshold by WHO and CDC guidelines. Additional analysis considered the occurrence of 1.5-fold serum creatinine increase from baseline and a composite outcome of creatinine clearance <60 mL/min or a 1.5-fold serum creatinine increase; a 1.5-fold increase in serum creatinine compared to baseline is a conservative measure often used in the context of acute kidney

injury. Results were summarized at an individual level as an unconfirmed or confirmed creatinine event. Cumulative frequency and patterns of occurrence of each creatinine outcome were determined separately for each study and are descriptively compared between the two cohorts. Cox proportional hazards regression models stratified by site were used to explore baseline factors independently associated with creatinine clearance <60 mL/min.

Results

Participant characteristics

Overall, 5358 participants were included in this analysis: 4404 (82% of all participants) from the Partners PrEP Study and 954 (94% of all participants) from the Partners Demonstration Project. The majority of participants were aged ≥30 years (mean age: 35 and 32 years for the Partners PrEP Study and the Demostration project, respectively) and approximately two thirds were male in both studies. The baseline mean creatinine clearance was 111 mL/min (110 mL/min in the Partners PrEP Study and 116 mL/min in Demostration project), and 22% of participants in the Partners PrEP Study and 13% in the Demonstration Project had a baseline creatinine clearance between 60–90 mL/min. Mean baseline weight was 61kg, and 22% of participants in the Partners PrEP Study and 9% in the Partners Demonstration Project weighed ≤55kg.

Creatinine clearance decline <60 mL/minute

The primary analysis considered the cumulative proportion of participants experiencing CrCl decline to <60mL/min during the first 12 months of PrEP use. In the clinical trial with 3-monthly monitoring: 1.4% of participants experienced a creatinine clearance level <60 mL/min at the first quarterly check, but fewer than 25% of these were confirmed upon repeat testing (i.e., 0.4% experienced a confirmed event). At month 6, 0.5% of participants experienced a confirmed event, and at month 12, 0.7% of participants had a confirmed event (Table 1). In the study with 6-monthy monitoring, 0.2% of participants experienced a confirmed creatinine clearance level <60min/mL at both month 6 and at month 12.

Frequency of 1.5-fold creatinine elevation compared to baseline

We observed a similar pattern when the analysis was based on a 1.5-fold creatinine elevation from baseline: At 6 months, 0.5% of participants in the clinical trial using 3-monthy creatinine monitoring and 0.3% of participants in the demonstration project using 6-monthy monitoring experienced a 1.5-fold creatinine elevation from baseline. At 12 months, 0.8% of participants in the clinical trial and 0.4% of participants in the demonstration project experienced a a 1.5-fold creatinine elevation. Similar patterns were observed when the analysis was based on a composite outcome (confirmed CrCl level <60mL/min or 1.5-fold creatinine elevation from baseline).

Creatinine-related PrEP hold and baseline factors associated with CrCl decline <60 mL/minute

Overall, 31 participants had confirmed creatinine clearance levels <60 mL/min within 12 months of PrEP initiation. An additional 21 experienced a confirmed event during 24 months of follow-up. For these 52 persons, 27 had a level between 50–60 mL/min and were allowed

to continue PrEP as per the protocol-specified safety management plan, 13 had PrEP temporarily withheld but restarted after resolution of the abnormality, 9 had PrEP withheld and were not able to restart within the pre-specified study follow up time, and in 3 persons the abnormality resolved but PrEP hold was continued due to other protocol specifications (pregnancy, HIV seroconversion, or study exit). Specifically, in the Demonstration Project, 2 people experienced confirmed CrCl decline <60 mL/Min on repeat testing. First, a 64-year-old male with baseline CrCl of 64 ml/min, experienced decline to 56 (serum creatinine: 1.05 mg/dL) at month 6. Study drug was discontinued and never restarted. CrCl at study exit was 52 ml/min. Second, a 29-year-old female experienced decline from a baseline of 61 ml/Min to 53 ml/Min at month 18. She continued on drug and CrCl was 59 mL/min at exit.

Overall, declines in creatinine clearance <60 mL/min were more likely to occur in participants who were >45 years (adjusted hazard ratio [aHR] 3.18, 95% CI 1.76–5.75), weighed ≤55 kg (aHR2.01, 95% CI 1.13–3.57), elevated blood pressure (aHR 2.57, 95% CI 0.98–6.78; p=0.06), and those who had a baseline creatinine clearance between 60–90 mL/min (aHR 22.50 95% CI 7.78–65.07). These factors were all independently associated with experiencing creatinine clearance decline to below 60 ml/min (Table 2). Women appeared to be marginally more likely to experience events compared to men, but this difference may be driven by gender-related physiological differences and lower muscle mass in women rather than underlying pathophysiological differences. Notably, even among those with at least one of these characteristics, only a minority (i.e. <5%) ever experienced a confirmed creatinine clearance <60 mL/min during 24-month follow-up: baseline creatinine clearance between 60–90 mL/min=4.3%; weighed ≤55 kg=1.9%; and ≥45 years=3.4% (Table 2).

Discussion

In these two large cohorts of HIV-uninfected participants with high adherence to daily TDF-based PrEP, the identification of moderate declines in creatinine clearance to a level <60 mL/min was not qualitatively different based on a 3-monthly or 6-monthly monitoring schedule. Overall, creatinine elevations were rare and most were not confirmed on repeat testing (<1% of participants had confirmed elevations). Thus, these data suggest that creatinine clearance monitoring on a 6-month schedule could be equally safe as a 3-month schedule and require fewer resources for a majority of persons receiving PrEP for up to 24 months. More frequent monitoring may be indicated for those with specific risk factors associated with high propensity for declines in creatinine clearance (e.g., age >45 years, baseline CrCl <90 mL/min, hypertension, and/or weight <55 kg); these characteristics have also been associated with increased likelihood of kidney dysfunction in other populations[15,16].

These data are encouraging for PrEP implementation programs, particularly in resource limited settings, where laboratory testing may be a burden to health systems. For example, in Kenya, recent Ministry of Health guidelines regarding PrEP are permissive of less frequent kidney monitoring,[17] recommending baseline and then annual serum creatinine but permitting PrEP to be initiated and continued without kidney testing if laboratory testing is not available. In these guidelines, testing for individuals >45 yrs, weight <55 kg, with

diabetes or hypertension, or other risk factors for renal disease is still strongly recommended. Guidelines that tailor the type of service, location and provider of service, and frequency of service to the differing needs of distinct patient groups will not only improve efficiency but are consistent with the differentiated care approach which has gained interest in ART programs.

Less frequent kidney monitoring may also be appealing to PrEP users. Given the epidemiology of HIV, persons for whom PrEP is most useful are likely to find it challenging to frequently undergo laboratory-based safety monitoring. Moreover, PrEP acceptability may be complicated by negative attitudes toward health systems and providers and by higher costs stemming from frequent safety monitoring and confirmatory testing. Thus, developing evidenced-based PrEP delivery models that minimize consumer burden is a priority for PrEP implementation. Approaches to maintain PrEP user interest by improving the efficiency of PrEP delivery may involve using point-of-care creatinine testing, reducing the frequency of kidney safety monitoring, incorporating HIV self-testing[18], and offering 6-monthly PrEP refill.

We qualitatively observed a slightly higher number creatinine-related abnormalities in the protocol with implementing 3 monthly testing than in 6-monthly which is likely driven by high volume of testing as only a minority of these events were confirmed with subsequent testing. We have previously reported that severe kidney toxicities are very rare (<2%) with TDF-based PrEP and that even the small declines in kidney function occurring in a minority of persons quickly resolve within weeks of discontinuing PrEP[3–5]. Our data thus are in agreement with the US Centers for Disease Control and Prevention recommendation for routine kidney monitoring every 6 months while using PrEP[19], and models that incorporate kidney monitoring even less frequently than biannually among healthy persons merit investigation.

This analysis has limitations. First, the two studies analyzed here were not specifically conducted to compare the frequency of kidney function testing. Nonetheless, the studies were conducted in similar populations during relatively similar time frames, and kidney function testing was performed by protocol in both studies. In addition, the low frequency of moderate declines in creatinine clearance even under exceptionally high adherence to daily dosing lends confidence to our findings. Second, this study only considered declines in creatinine clearance <60 mL/min and not other changes that could be considered clinically relevant, such as a decline from normal to a creatinine clearance <90 mL/min. Changes in creatinine clearance above 60mL/min are subject to limitations of the estimating equation, and may not have triggered confirmatory testing in all cases. Third, both study populations were generally healthy, and optimal kidney function monitoring in persons with co-morbid conditions like diabetes, hypertension, or use of nephrotoxic medications is unknown. Fourth, follow-up time was limited to 24 months, and studies in HIV-infected persons suggest that TDF toxicity is cumulative; as a result, this analysis does not provide guidance on the optimal frequency of kidney function monitoring in persons who plan to take TDF-based PrEP for longer periods. Finally, this study did not consider the frequency or necessity of monitoring for proximal tubular dysfunction with TDF-based PrEP. While we previously demonstrated no statistically significant difference in the incidence of proximal tubular

dysfunction between participants randomized to TDF-based PrEP versus placebo[4], we did identify a single case of overt proximal tubular dysfunction in the clinical trial population; this participant was identified on the basis of routine creatinine clearance testing during the trial[4].

In conclusion, in these two large cohorts of HIV-uninfected persons using PrEP, moderate decline in creatinine clearance was rare over up to 24 months of follow-up, and the pattern of identification was not qualitatively different based on 3-monthly or 6-monthly safety monitoring. Delivery of PrEP to most healthy persons can likely be implemented with 6-monthly and the potential for less frequent kidney safety monitoring can be explored through routine data collected via PrEP delivery programs.

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Table 1

Cumulative proportion of persons experiencing creatinine elevation, according to study and follow-up month

	Partners PrEP Study: 3-monthly monitoring (n=4404)			Partners Demonstration Project: 6-monthly monitoring (n=954)	
Study month	**3**	**6**	**12**	**6**	**12**
CrCl <60 mL/min, n (%)					
Unconfirmed	1.4% (63/4404)	2.0% (880/4404)	2.7% (120/4404)	0.7% (7/954)	1.1% (10/954)
Confirmed[*]	0.4% (16/4404)	0.5% (21/4404)	0.7% (29/4404)	0.2 (2/954)	0.2% (2/954)
>1.5 fold change SCr elevation, n (%)					
Unconfirmed	1.3% (57/4404)	1.9% (85/4404)	2.8% (123/4404)	1.4% (13/954)	1.8% (17/954)
Confirmed[*]	0.4% (18/4404)	0.5% (23/4404)	0.8% (33/4404)	0.3% (3/954)	0.4% (4/954)
Composite outcome: Confirmed CrCl <60 mL/min or >1.5-fold increase from baseline n (%)	0.8% (33/4404)	0.9% (40/4404)	1.3% (58/4404)	0.4% (4/954)	0.5% (5/954)

[*] Abnormality confirmed with repeat testing mostly with 1 week.

Scr, serum creatinine, CrCl creatinine clearance

Table 2

Association of baseline covariates with any confirmed decline in CrCl <60 mL/min

			Adjusted hazard ratios comparing those with the characteristic to those without** (95% CI); p= values	
Baseline characteristic	***Unconfirmed CrCl <60 mL/min, %****	***‡Confirmed CrCl <60 mL/min, %****	***Overall***	***For events occurring within 12 months of PrEP initiation***
Sex				
Female (n=1956)	7.6%	1.9%	1.92 (0.97, 3.79); p=0.06	6.57 (1.85, 23.30); p=0.004
Male (n=3402)	1.1%	0.4%		
Age — years				
≥45 (n=676)	9.9%	3.4%	3.18 (1.76, 5.75); p<0.001	2.66 (1.23, 5.73); p=0.01
<45 (n=4682)	2.5%	0.6%		
Weight — kg				
≤55 (n=1601)	6.3%	1.9%	2.01 (1.13, 3.57); p=0.017	1.63 (0.78, 3.38); p=0.19
>55 (3757)	2.3%	0.6%		
Systolic blood pressure — mmHg				
≥140 (n=274)	2.55%	1.8%	2.57 (0.98, 6.78); p=0.06	2.47 (0.56, 10.95); p=0.23
<140 (n=5084)	3.5%	0.9%		
CrCl — mL/min				
60–90 (n=1105)	14.7%	4.3%	22.50 (7.78, 65.07); p<0.001	44.11 (5.84, 333.27); p<0.001
>90 (n=4253)	0.6%	0.1%		

*Row percent

**Cox regression model stratified by site.

‡Abnormal testing confirmedon repeat measurement, mostly done within 1 week.

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