Published in final edited form as:

Lancet HIV. 2016 November ; 3(11): e521–e528. doi:10.1016/S2352-3018(16)30153-9.

Age, baseline kidney function, and medication exposure are associated with declines in creatinine clearance on PrEP: an observational cohort study

Monica Gandhi, MD [Full Professor],
Division of HIV, Infectious Diseases, and Global Medicine; Department of Medicine, University of California, San Francisco (UCSF), 995 Potrero Avenue, Building 80, 4th floor, San Francisco, CA 94110, 415-476-4082 x 127; monica.gandhi@ucsf.edu

David Glidden, PhD [Full Professor],
Department of Biostatistics and Epidemiology, UCSF, Box 0560, 550 16th Street, San Francisco, CA 94158, David.glidden@ucsf.edu

Kenneth Mayer, MD [Full Professor],
Fenway Health, 1340 Boylston Street, Boston, MA 02215, kmayer@fenwayhealth.org

Mauro Schechter, MD [Full Professor],
Projeto Praça Onze, Hospital Escola São Francisco de Assis, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, Mauro.schechter@gmail.com

Susan Buchbinder, MD [Full Professor],
San Francisco Department of Public Health, 25 Van Ness Avenue, Suite 710, San Francisco, CA 94102, Susan.buchbinder@sfdph.org

Beatriz Grinsztejn, MD,
Instituto de Pesquisa Clinica Evandro Chagas (IPEC) CRS, Av. Brasil, 4365, Manguinhos, RJ CEP: 21040-900, Beatriz.grinsztejn@gmail.com

Sybil Hosek, PhD,
Department of Psychiatry, Stroger Hospital of Cook County, 1900 W. Polk Street, #854, Chicago, IL 60612, sybilhosek@gmail.com

Martin Casapia, MD,
Asociacion Civil Selva Amazonica (ACSA) CRS, Urb. Jardin N 27, Iquitos, Peru, mcasapia@acsaperu.org

Correspondence to: Monica Gandhi.

Authors contributions:
M.G., D.G., A.L, K.M. and R.M.G. contributed substantially to the analyses in the paper with D.G. performing all of the statistical analyses. R.M.G. is the PI of iPrEx OLE and D.G., K.M., M.S., S. B., B.G., S.H., M.C, J.G., L.B, and A.L. contributed substantially to the data collection and analyses of the study. A.L., H.H. M.G., and L.Z.B. either directed or performed the hair assay work at UCSF. M.G. and D.G. drafted the initial manuscript with all authors contributing substantially to its development.

Meeting at which this work was presented:
Conference on Retroviruses and Opportunistic Infections, February 22–25, 2016; Boston, MA; Abstract 866

Ethics committee approval: The study protocol was approved by Institutional Review Boards of all participating sites and all participants provided written informed consent in their preferred language.

Juan Guanira, MD,
Investigaciones Médicas en Salud, Jr. Risso 390 Lince, Lima, Peru, jguanira@inmensa.org

Linda-Gail Bekker, PhD [Full Professor],
Desmond Tutu Health Foundation, Level One, Wernher Beit North, Faculty of Health Sciences, Anzio Rd, Observatory, 7925, Cape Town, South Africa, Linda-gail.bekker@hiv-research.org.za

Alexander Louie, BA,
Department of Medicine, UCSF, 513 Parnassus Avenue, Med. Sci. Room 907, San Francisco, CA 94143, Alexander.louie@ucsf.edu

Howard Horng, PhD,
Department of Bioengineering and Therapeutic Sciences, UCSF, 513 Parnassus Avenue, Med. Sci. Room 907, San Francisco, CA 94143, Howard.horng@ucsf.edu

Leslie Z. Benet, PhD [Full Professor],
Department of Bioengineering and Therapeutic Sciences, UCSF, 533 Parnassus Avenue, UC Hall Room 068A, San Francisco, CA 94143, Leslie.benet@ucsf.edu

Albert Liu, MD, and
HIV Prevention Intervention Studies Bridge HIV, San Francisco Department of Public Health, 25 Van Ness Avenue, Suite 100, San Francisco, CA 94102, albert.liu@sfdph.org

Robert Grant, MD, MPH [Full Professor]
Division of Pulmonary and Critical Care Medicine, Department of Medicine, UCSF, 1650 3rd Street, San Francisco, CA 94158, Robert.grant@ucsf.edu

SUMMARY

Background—As pre-exposure prophylaxis (PrEP) with tenofovir-disoproxil-fumarate/emtricitabine (TDF/FTC) for the prevention of HIV infection enters a phase of global roll-out, strategies to maintain effectiveness, but minimize adverse effects, merit close consideration. The aim of this study was to evaluate rates and predictors of renal toxicity in a large open-label study of PrEP to help provide guidance on safety monitoring with this important prevention strategy.

Methods—The iPrEx open-label-extension (OLE) study (NCT00458393) enrolled HIV-negative MSM/transgender participants from three previous PrEP trials from Brazil, Ecuador, Peru, South Africa, Thailand, and the U.S into an open-label PrEP study. There were no restrictions on current renal function for enrollment into iPrEx OLE.. Creatinine clearance (CrCl) on PrEP was estimated every 12 weeks and in a subset, hair samples were collected for measuring tenofovir (TFV)/FTC concentrations via liquid-chromatography/tandem-mass-spectrometry. Change in CrCl from baseline was calculated and predictors identified.

Findings—Baseline characteristics of participants in iPrEx-OLE (n=1224; 7475 person-visits) and its hair substudy (n=220; 1114 person-visits) were similar. Over 72 weeks (median), the average decline in CrCl was −2·9% (p<0.0001), but declines were significantly greater for those starting PrEP at older ages (−4·2% (95% CI −2·8%, −5·5%), baseline age 40–50 years; −4·9% (−3·1%, −6·8%), age ≥50). Besides age, baseline CrCl of <90ml/min in multivariate models predicted renal decline. There was a monotonic relationship between percent decrease in CrCl and number of doses of TDF/FTC taken per week as estimated by hair levels (p 0.008).

Interpretation—With the global roll-out of PrEP, our analysis suggests that the frequency of safety monitoring may differ by age group and that pharmacologic measures of adherence can additionally monitor for toxicities.

Funding—NIH

Keywords

HIV prevention; pre-exposure prophylaxis; PrEP; pharmacologic measures; tenofovir/emtricitabine; hair concentrations; iPrEx Open Label Extension (OLE); renal decline; creatinine clearance

INTRODUCTION

The efficacy of pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) to prevent HIV acquisition has been demonstrated in multiple trials and PrEP is now broadly recommended by the Centers for Disease Control and Prevention (CDC) and the World Health Organization. As PrEP enters the phase of global roll-out, strategies to optimize effective use while minimizing adverse effects merit closer consideration. Although toxicities to TDF/FTC-based PrEP have been few and generally reversible in studies to date[1,2], the optimal frequency for safety monitoring with long-term exposure has not been established. Identifying subgroups of individuals who might warrant more (or less) intensive safety monitoring during PrEP will facilitate its safe scale-up.

Several PrEP trials or demonstration projects have shown modest but statistically significant declines in renal function with administration of daily TDF/FTC, including the global iPrEx trial[3], Partners PrEP[4], Bangkok TDF[5], and the U.S. PrEP Demonstration Project[6]. The duration of follow-up in these studies was ≤36 months and the average decline in renal function measured by estimated creatinine clearance (CrCl) in iPrEx was 2·4%[3]. The incidence of serious renal events in PrEP trials has been low. Moreover, in iPrEx and Partners PrEP, declines in renal function were mostly reversible 4–20 weeks after discontinuation[3,7].

With TDF/FTC-based treatment, greater declines in renal function are associated with longer duration of TDF use[8–11], as well as older age[8,12,13] or lower baseline renal function[11,14] at TDF initiation. In the placebo-controlled efficacy trials of PrEP, baseline renal function was required to be within normal range prior to randomization, and trial participants were generally young. Open-label studies and demonstration projects of PrEP allow the toxicities of this preventative strategy to be evaluated under more generalizable conditions. In this analysis, we define subgroups of individuals in the iPrEx open label extension (OLE) study[15] - a cohort of men-who-have-sex-with-men (MSM) and transgender women on PrEP who were former participants of PrEP trials and then enrolled into iPrEx OLE - with varying risks of renal decline.

In a subset of iPrEx OLE participants, we additionally examine the impact of long-term exposure to tenofovir (TFV), the active moiety of TDF, and FTC, both assessed via hair concentrations[16], on renal function. Higher exposure to TFV/FTC during treatment,

generally assessed by plasma levels, has been associated with renal toxicities[17,18]. Prior studies by our group have shown a linear relationship between oral TDF dose and concentrations of TFV in hair[16]. In this study, for the first time in either the PrEP or treatment setting, we examine the effects of long-term exposure to TFV and FTC, assessed via hair concentrations, on subsequent renal function.

METHODS

Study population

iPrEx OLE enrolled 1225 HIV-negative MSM and transgender women (all male at birth) from Brazil, Ecuador, Peru, South Africa, Thailand, and the U.S who previously enrolled in three PrEP trials into an open-label PrEP study without restrictions on current renal function[15]. Serum creatinine (Cr) was measured every 12 weeks and CrCl – the parameter recommended for safety monitoring by CDC guidelines[19]- estimated by the Cockcroft-Gault equation.[20] Analyses were repeated with the outcome of estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) equation.[21]

Procedures

Hair samples were collected from a subset of participants every 12 weeks, which involved cutting ~100 strands of hair from the occipital scalp[16]. Hair was not collected on all 1224 participants in iPrEx OLE due to site and protocol constraints. Of the participants offered hair sampling in iPrEx OLE (324), 68% agreed to hair collection. The reasons for declining in the remaining 32% included concerns about appearance, not having enough hair, not having enough time, concerns about pain, religious reasons or no reason provided. Self-reported adherence to study drug was assessed by survey. The study protocol was approved by Institutional Review Boards of all participating sites and all participants provided written informed consent in their preferred language. Results of hair testing were not reported back to participants.

After storage and shipment at ambient temperature to our University of California San Francisco (UCSF)-based “Hair Analytical Laboratory” (HAL), the proximal 1·5 centimeter of each hair sample (representing ~6 weeks exposure) was cut finely with scissors and 5 milligrams (mg) processed and analyzed using liquid-chromatography/tandem-mass-spectrometry (LC-MS/MS)[16]. The assays for measuring TFV and FTC in hair samples have been peer-reviewed and approved by the Division of AIDS Clinical Pharmacology and Quality Assurance (CPQA) program.

Statistical analysis

The percent change in CrCl from the baseline value at each timepoint was estimated (mean ± standard error (SE)) from a linear mixed effects model for all iPrEx OLE participants, adjusted for age, baseline CrCl, and site of enrollment. Participants were censored at the time of permanent PrEP discontinuation if prior to the end of the study period. The probability of CrCl falling to ≤60 ml/min (as the threshold at which TDF/FTC-based PrEP should be discontinued per CDC guidelines[19]) at least once over the duration of the study was calculated among participants whose baseline CrCl was above that level. The analysis

was repeated to examine the probability of CrCl falling to ≤70 ml/min, a value defined as "renal impairment" and "a point at which people with decreasing eGFR could be switched away from potentially nephrotoxic antiretrovirals" in a large recently-published study examining risk factors for kidney disease among HIV-infected individuals[11]. The rate of the CrCl value falling to ≤60ml/min or ≤70 ml/min was calculated per quarterly visit over the course of the study and an annualized rate, or the probability of at least one value of CrCl falling to ≤60ml/min or ≤70 ml/min over four quarterly visits, was then reported. We then modeled this rate in a Poisson regression with terms for baseline age, baseline CrCl (stratified into <90 or ≥90 ml/min[11]), and quartile of TFV or FTC concentration in hair for those who underwent hair sampling. Data from the STRAND study[16], where TDF was given to HIV-uninfected volunteers via directly observed dosing of 2, 4 and 7 doses/week for 6 weeks each (with washout periods in-between) provided estimates for TFV concentrations in hair consistent with different dosing patterns. In STRAND, hair concentrations of TFV were linearly associated with number of doses per week.

Role of the funding source

The funder of the study (National Institutes of Health) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Gilead Sciences donated study drug and had no input into the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Of 1224 participants (7475 person-visits) who received PrEP in iPrEx OLE with renal data available (only 1 with missing data), 220 were in the hair substudy (1114 person-visits). Table 1 shows the baseline characteristics of participants in iPrEx OLE and its hair substudy, including age, gender identity (cis MSM/transgender women), race/ethnicity, body mass index (BMI), baseline creatinine clearance, baseline hypertension (systolic blood pressure >140mmHg or diastolic blood pressure >90 mmHg), prevalence of NSAID use in the prior 30 days, and self-reported adherence to PrEP drugs. The baseline characteristics of the participants in the hair substudy were similar to those in the entire sample. The study was conducted from September 2011–December 2013.

Over the duration of the study (median 72 weeks, IQR 71 to 73), the average decline in CrCl for all participants in iPrEx OLE was −2·9% (95% CI: −2·4% to −3·4%), p<0.0001 for trend. The mean absolute difference in CrCl over the duration of the study was −4.2 (95% CI: −3.6 to −4.7) ml/min. Declines in CrCl were significantly greater over time in participants who started PrEP at older ages: −2·6% decline (95% CI: −2·4% to −3·4%) in those with baseline age <40 years; −4·2% (95% CI: −2·8% to −5·5%) decline with starting age 40–50 years (p<0·001 in comparison to <40 years); −4·9% decline (95% CI: −3·1% to −6·8%) with baseline age ≥50 years (p<0·001) (Figure 1) when adjusted for baseline CrCl.

Declines in CrCl over time were significantly greater in those who started with higher CrCl at baseline. There was a +3·2% (+2·1 to +4·3) increase in those who started PrEP in the lowest quartile of baseline CrCl (56–100 ml/min); −2·0% (−3·1 to −0·9) decrease in those

starting in the 2nd quartile (101–113 ml/min); −3·6% (−4·7 to −2·5) in those starting in the 3rd quartile (114–128 ml/min); and −10·0% (−11·2 to −8·8), p < 0·0001 in those who started in the highest quartile of baseline CrCl (129–208 ml/min). In a multivariate model examining predictors of declining CrCl, including age, starting CrCl, hypertension, BMI and recent NSAID use, only baseline CrCl and baseline age showed significant associations.

The rate of CrCl falling to ≤60 ml/min (which was a protocol-defined criterion for stopping PrEP) was low at 0.1% overall in the cohort across all visits (9 of 7198 visits), but all 9 of the drops occurred in participants who started PrEP at CrCl <90ml/min (4·8% annualized rate in this group) and 8/9 occurred in participants starting PrEP ≥50 years of age (4·3% annualized rate). The rate of CrCl falling to ≤70 ml/min occurred in 47 of 7198 visits, yielding a 2·6% annualized rate (95% CI: 1·9% to 3·4%). In participants < 40 years at baseline, CrCl fell to ≤70 ml/min infrequently (7/5686 visits -- 0·5% annualized rate), but the relative risk of this fall was significantly higher in participants who started PrEP at older ages (RR 13·4 (95% CI 5·5 to 32·5, p < 0·001 for 40–50 years; RR 36·6 (95% CI 15·6 to 83·9 p <0·001 for >50 years) or those who started PrEP with lower renal function at baseline (RR 31·2 (95% CI 16·2–60.1, p <0·001), baseline CrCl ≤90ml/min versus >90ml/min) (Table 2). Of 47 incidents where CrCl fell to ≤70ml/min in the cohort, the creatinine was rechecked 3 months later in 43 and the CrCl remained ≤70ml/min in 15 (35%) of incidents.

Approximately 27% (296/1114) of person-visits had hair levels demonstrating no detectable PrEP use; 16% of visits (n=173) had levels consistent with <2 pills per week; 9% (n=102) had levels consistent with 2–3 pills per week; 33% (n=366) had levels consistent with 4–6 pills per week; and 16% (n=177) had levels consistent with daily dosing. The median self-reported adherence in the visits where no drug was detected was 73% (Table 1).

There was a monotonic relationship between percent decrease in CrCl and increasing quartile of TFV (p 0·008 for trend) or FTC concentrations (p 0·006 for trend) in hair. For instance, the mean % change in CrCl from baseline over the duration of the study (median 72 weeks) was −3·6% (95% CI −1·7% to −5·5%) when hair levels indicated dosing of <2 doses/week but −4·8% (95% CI −2·7% to −6·5%) when hair levels indicated 7 pills per week (Figure 2). There was no difference in mean changes in CrCl between those taking 4–6 pills per week compared with 7 per week (p=0·93).

For participants in the hair substudy, the percentage of visits where CrCl fell to ≤60ml/min or ≤70ml/min were both low (0.1% and 1.1%, respectively), but the relative risks of both events were higher when participants started PrEP when >50 years or at baseline CrCl of <90ml/min (Table 2). Those with a TFV or FTC hair concentration in the highest quartile (commensurate with use of 6·4 (5·9 to 6·9) tablets per week) also demonstrated a trend towards a higher relative risk of the CrCl falling to ≤70ml/min (p trend=0·19 for TFV and 0·004 for FTC). In a multivariate model examining predictors of declining CrCl, including age, starting CrCl, hypertension, BMI, NSAID use, and hair concentrations of drug, only baseline CrCl, baseline age and FTC level in hair were significantly associated.

Similar results were seen when analyses, both in the entire iPrEx OLE cohort and the participants in the hair substudy, were repeated with the outcome of renal function

calculated by the MDRD equation (eGFR)[21] instead of via the Cockcroft-Gault equation (CrCl)[20] (data not shown).

DISCUSSION

As in previous studies examining the impact of PrEP on renal function[4–6,22], there was a modest but statistically significant decrease in estimated creatinine clearance over time in iPrEx OLE, an effect most pronounced in those starting PrEP at older ages (Figure 1). Moreover, for the first time in any setting (treatment or prevention), we show that higher concentrations of TFV and FTC in hair samples are associated with greater declines in renal function. This decline was monotonically associated with numbers of doses of TDF/FTC taken per week as estimated by hair levels (Figure 2). Finally, the probability of CrCl falling to ≤60 ml/min or ≤70 ml/min at least once over the first year on PrEP was low, but also elevated when participants started PrEP at older ages or with a starting CrCl ≤90ml/min (Table 2). In sum, our results suggest that renal monitoring on PrEP for those without concomitant risk factors for renal disease may be most important in older PrEP users (> 40 years) and those with marginal renal function at baseline.

Pharmacologic exposure measures, where drug levels are monitored in a biomatrix such as plasma, peripheral blood mononuclear cells (PBMCs), dried blood spots (DBS) or hair, are of increasing interest to the field of PrEP adherence monitoring. Indeed, given the limitations of self-reported adherence[23], pharmacologic measures have been crucial for trial interpretation in PrEP studies[24,25]. In this study, as in many others, self-reported adherence correlated poorly with adherence adjudicated by pharmacologic measures. For instance, at the same visits where no PrEP drugs were detected in hair samples, the median self-reported adherence was 73% (Table 1).

Pharmacologic measures measure behavior (e.g. adherence or drug-taking), but also monitor pharmacokinetic variability in drug concentrations, serving as a direct assessment of exposure, either short or long-term, depending on the matrix. For example, plasma measures of drug assess exposure over days, whereas drug concentrations in PBMCs assess exposure over weeks[26]. PrEP drug concentrations in DBS[27] and hair[16] represent longer-term measures of exposure- over weeks to months- are highly correlated[28], and TFV-DP and FTC-triphophate (FTC-TP) concentrations in DBS were strongly associated with protective efficacy in iPrEx OLE[15].

While useful in assessing adherence, pharmacologic measures can also monitor for toxicities. In this study, hair concentrations of TFV/FTC predicted renal decline. In the iPrEx trial, higher concentrations of intracellular TFV-DP in PBMCs were associated with greater losses in bone mineral density[29], and drug detection in plasma or PBMCs were associated with greater declines in CrCl[22]. Hair is easy to collect, store and analyze and does not require a cold chain or biohazardous precautions. The current study adds to the growing literature around the utility of hair monitoring in TDF/FTC-based PrEP.

The CDC Clinical Practice Guidelines[19] recommends biannual monitoring of creatinine during PrEP in those without other risk factors for renal insufficiency and cessation if the

CrCl falls below 60ml/min. For participants under 40 years of age in iPrEx OLE, the mean decline in CrCl over the duration of the study was modest (−2·6%) (Figure 1) and no patients experienced a CrCl drop to ≤60ml/min (Table 2), even in those with estimated daily dosing. In younger patients, therefore, monitoring CrCl less frequently may be reasonable. Older age or a lower baseline creatinine clearance (≤90ml/min) at the initiation of PrEP were each independently associated with a faster rate of renal decline or a risk of CrCl falling ≤60ml/min or ≤70ml/min, especially with daily dosing, so more intensive safety monitoring in patients with these baseline characteristics may be indicated. Other treatment settings have shown similar risk factors (age and marginal renal function) for TDF-associated toxicity[8–14] and two other PrEP studies have shown that older age predicts greater declines in renal function on PrEP.[5,6]

Of note, as with TDF/FTC-based treatment[11], greater declines in renal function on TDF/FTC-based PrEP were seen in those who started with the highest baseline CrCl. Our analysis suggests that this trend may reflect regression toward the mean, in that there was an increase in CrCl among those starting PrEP in the lowest quartile of baseline CrCl.

Finally, since a substantial number of patients in this study did not take PrEP drugs daily according to the hair level analyses (and 27% did not take drug at all), the mean decrease in creatinine clearance in this population may underestimate rates in populations with optimal adherence. In iPrEx OLE, 4–7 doses a week were associated with similar rates of protection[15] and toxicity (Figure 2). Although protective efficacy was high with “on demand” dosing of PrEP before and after sex in one study[30], daily oral dosing is recommended in the United States[19], providing the highest concentrations of drug and the most forgiveness for missed doses. Although the on-demand PrEP regimen studied in iPERGAY has not been approved by many regulatory authorities, the data in this study should spark further investigation of PrEP strategies for older patients with an increased risk for renal impairment since less than daily dosing might allow for protection, while maximizing safety.

The relatively short duration of follow-up for this study is a limitation when extrapolating findings to the real-world roll-out of PrEP. Long-term follow-up will be needed to monitor for long-term toxicities. Moreover, iPrEx OLE enrolled only former participants of clinical PrEP trials, which all required normal renal function at baseline. Even though entrance to the open-label extension phase did not require normal renal function, this original limitation still restricts generalizability. This study does not provide insight into the risks and minimum frequency of renal monitoring required to maintain safety among people starting PrEP with baseline renal insufficiency, or who have comorbidities associated with renal disease. Moreover, this analysis of estimated creatinine clearance only has implications for glomerular function, but not tubular function. Finally, hair measures provide a cumulative measure of exposure (over 6 weeks in this study), but cannot assess gradations of recent or intermittent use.

At present, since there is no alternative agent approved for PrEP beyond TDF/FTC, no option for PrEP in individuals with a CrCl ≤60 ml/min, and no data on the long-term effects of PrEP on those with borderline renal function, research to identify the minimum frequency

of renal monitoring required for the safe use of TDF/FTC-based PrEP is needed. Our results suggest that these minimum monitoring requirements may differ by age, baseline renal function and adherence. We further demonstrate – in a large cohort of MSM and transgender women–that declines in renal function were higher with greater exposure to TFV/FTC (as assessed via hair concentrations). The provision of PrEP to all at-risk individuals worldwide is integral to ending the HIV epidemic and approaches to maximize efficacy and minimize adverse effects, including the possible incorporation of pharmacologic measures to monitor both adherence and toxicities, will aid in effective scale-up.

Acknowledgments

The authors thank the participants in the iPrEx OLE study and the dedicated study staff. We thank the Hair Analytical Laboratory at UCSF for work on the hair assays, as well as Stephen May for his excellent research coordination work. We acknowledge and are eternally grateful to Hao Zhang MD (program officer at NIAD for R01 AI098472) for his invaluable support and scientific input.

Conflicts of interest:

Gilead Sciences donated FTC/TDF for participants in the study, but provided no other financial support and did not contribute to data interpretation or manuscript development. VIIV has provided research funding to RMG for a competing PrEP product not discussed in the letter and DVG is a member of a DSMB for a VIIV-sponsored trial.

Role of funding source:

This work was supported by the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), as a cooperative agreement (UO1 AI84735 to Dr. Anderson, UO1 AI64002, 2R01 AI062333 to Dr. Grant and UM1 AI068619). NIAID additionally supported the hair assays for this work (R01 AI098472, P.I. Gandhi) and data analysis (R03 AI120819, R03 AI122908, P.I. Glidden). U01 AI034989 (WIHS, P.I. Greenblatt) supported positive controls and reagents for the hair assays.

REFERENCES

1. Mugwanya KK, Baeten JM. Safety of oral tenofovir disoproxil fumarate-based pre-exposure prophylaxis for HIV prevention. Expert Opin Drug Saf. 2016; 15(2):265–273. [PubMed: 26634852]
2. Grant, RM.; Mulligan, K.; McMahan, V., et al. Recovery of Bone Mineral Density After Stopping Oral HIV Preexposure Prophylaxis. Conference of Retroviruses and Opportunistic Infections (CROI); 2016 February 23–26; Boston, MA. 2016. (abstract 48LB)
3. Solomon MM, Lama JR, Glidden DV, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. Aids. 2014; 28(6):851–859. [PubMed: 24499951]
4. Mugwanya KK, Wyatt C, Celum C, et al. Changes in glomerular kidney function among HIV-1-uninfected men and women receiving emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis: a randomized clinical trial. JAMA Intern Med. 2015; 175(2):246–254. [PubMed: 25531343]
5. Martin M, Vanichseni S, Suntharasamai P, et al. Renal function of participants in the Bangkok tenofovir study--Thailand, 2005–2012. Clin Infect Dis. 2014; 59(5):716–724. [PubMed: 24829212]
6. Liu, A.; Vittinghoff, E.; Anderson, P., et al. Changes in Renal Function Associated with TDF/FTC PrEP Use in the US Demo Project. Conference of Retroviruses and Opportunistic Infections (CROI); 2016 February 23–26; Boston, MA. 2016. (abstract 867)
7. Mugwanya KK, Wyatt C, Celum C, et al. Reversibility of Glomerular Renal Function Decline in HIV-Uninfected Men and Women Discontinuing Emtricitabine-Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis. Journal of acquired immune deficiency syndromes. 2016; 71(4):374–380. [PubMed: 26914909]

8. Casado JL, Del Rey JM, Banon S, et al. Changes in kidney function and in the rate of tubular dysfunction after tenofovir withdrawal or continuation in HIV-infected patients. Journal of acquired immune deficiency syndromes. 2016
9. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. Aids. 2012; 26(7):867–875. [PubMed: 22313955]
10. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis. 2013; 207(9):1359–1369. [PubMed: 23382571]
11. Mocroft A, Lundgren JD, Ross M, et al. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. Lancet HIV. 2016; 3(1):e23–e32. [PubMed: 26762990]
12. Monteiro N, Branco M, Peres S, Borges F, Mansinho K. The impact of tenofovir disoproxil fumarate on kidney function: four-year data from the HIV-infected outpatient cohort. Journal of the International AIDS Society. 2014; 17(4 Suppl 3):19565. [PubMed: 25394072]
13. Mocroft A, Lundgren JD, Ross M, et al. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. PLoS Med. 2015; 12(3):e1001809. [PubMed: 25826420]
14. Zachor H, Machekano R, Estrella MM, et al. Incidence of stage 3 chronic kidney disease and progression on tenofovir-based regimens: A cohort study in HIV-infected adults in Cape Town, South Africa. Aids. 2016; 30(8):1221–1228. [PubMed: 26836786]
15. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. 2014
16. Liu AY, Yang Q, Huang Y, et al. Strong Relationship between Oral Dose and Tenofovir Hair Levels in a Randomized Trial: Hair as a Potential Adherence Measure for Pre-Exposure Prophylaxis (PrEP). PloS one. 2014; 9(1):e83736. [PubMed: 24421901]
17. Rodriguez-Novoa S, Labarga P, D'Avolio A, et al. Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations. Aids. 2010; 24(7): 1064–1066. [PubMed: 20299966]
18. Ezinga M, Wetzels JF, Bosch ME, van der Ven AJ, Burger DM. Long-term treatment with tenofovir: prevalence of kidney tubular dysfunction and its association with tenofovir plasma concentration. Antivir Ther. 2014; 19(8):765–771. [PubMed: 24584104]
19. Centers for Disease Control (CDC). Preexposure Prophylaxis for the Prevention of HIV in the United States: A Clinical Practice Guideline. 2014. http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1):31–41. [PubMed: 1244564]
21. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130(6):461–470. [PubMed: 10075613]
22. Solomon MM, Lama JR, Glidden DV, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. Aids. 2014
23. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. Journal of Acquired Immunodeficiency Syndromes (JAIDS). 2006; 43(Suppl 1):S79–S87.
24. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2012; 367(5):411–422. [PubMed: 22784040]
25. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine. 2015; 372(6):509–518. [PubMed: 25651245]
26. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012; 4(151):151ra25.

27. Castillo-Mancilla JR, Zheng JH, Rower JE, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS research and human retroviruses. 2013; 29(2):384–390. [PubMed: 22935078]

28. Gandhi M, Glidden DV, Liu A, et al. Strong Correlation Between Concentrations of Tenofovir (TFV) Emtricitabine (FTC) in Hair and TFV Diphosphate and FTC Triphosphate in Dried Blood Spots in the iPrEx Open Label Extension: Implications for Pre-exposure Prophylaxis Adherence Monitoring. J Infect Dis. 2015; 212(9):1402–1406. [PubMed: 25895984]

29. Mulligan K, Glidden DV, Anderson PL, et al. Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, Placebo-Controlled Trial. Clin Infect Dis. 2015; 61(4):572–580. [PubMed: 25908682]

30. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. The New England journal of medicine. 2015; 373(23):2237–2246. [PubMed: 26624850]

RESEARCH IN CONTEXT

Evidence before this study

The efficacy of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)-based pre-exposure prophylaxis (PrEP) for the prevention of HIV acquisition is now well-established. In the context of global roll-out and long-term use, the focus is now shifting to implementation, as well as defining predictors of adverse effects and developing algorithms for safety monitoring. To find other reports of renal toxicities on PrEP, we searched PubMed and abstracts from the Conference on Retroviruses and Opportunistic Infections (CROI) since January 1, 2008 with the search terms “Pre-exposure prophylaxis” or “PrEP” and “kidney” or “renal”. We also searched the HIV treatment literature starting from January 1, 2002 for risk factors associated with TDF/FTC-based toxicities with search terms such as “HIV”, “tenofovir”, “tenofovir disoproxil fumarate”, “emtricitabine”, “kidney”, “renal”, “tubular”. Several studies showed small declines in renal function in either placebo-controlled clinical trials with the use of TDF/FTC-based PrEP (global iPrEx trial, Partners PrEP trial, Bangkok TDF) or an open-label study (the U.S. PrEP Demonstration Project). A larger number of studies in cohorts of HIV-infected patients on TDF/FTC based treatment in HIV-infected individuals have shown renal decline and defined risk factors associated with subsequent renal insufficiency, including older age, a lower baseline renal function when starting therapy, or a longer period of time on TDF/FTC.

Added value of this study

Hair concentrations of drug serve as an integrated measure of behavior (adherence) and biology (pharmacokinetics) and prior studies have shown a strong linear relationship between TDF dose and hair concentration. This current study examines declines in renal function and predictors of that decline in a large open-label study of PrEP, and is the first to incorporate a long-term measure of pharmacologic exposure to PrEP drugs (using hair levels) as a predictor of toxicities. In this study based in the iPrEx open label extension (OLE) study (MSM and transgender women), we show that three important factors predict subsequent renal decline: 1) Older age when starting PrEP (>40 years); 2) Lower estimated creatinine clearance (<90 ml/min) when starting PrEP; and 3) Higher hair concentrations of tenofovir/emtricitabine. Mean changes in renal decline were significantly greater when hair concentrations showed that pill taking was consistent with 4–7 doses per week than with <4 doses per week. For those who started PrEP at ages <40 years with normal baseline renal function, the rate of clinically-significant drops in renal function over 72 weeks was minimal.

Implications of all the available evidence

Our study, in the context of existing evidence to date on rates of renal decline on TDF/FTC-based PrEP, has implications for guidelines for safety monitoring during the global roll-out of PrEP. For those starting PrEP at younger ages (<40 years) with high baseline renal function (CrCl >90 ml/minute), creatinine monitoring can likely be spaced out to yearly or even longer. For those starting PrEP at older ages (≥40 years), especially if the baseline renal function is lower than 90ml/min, creatinine monitoring should be more

frequent. Finally, this study incorporates a long-term measure of TFV/FTC exposure using hair levels to predict toxicities to PrEP for the first time, which has implications for the incorporation of pharmacologic measures of adherence/exposure to PrEP during the global expansion phase.

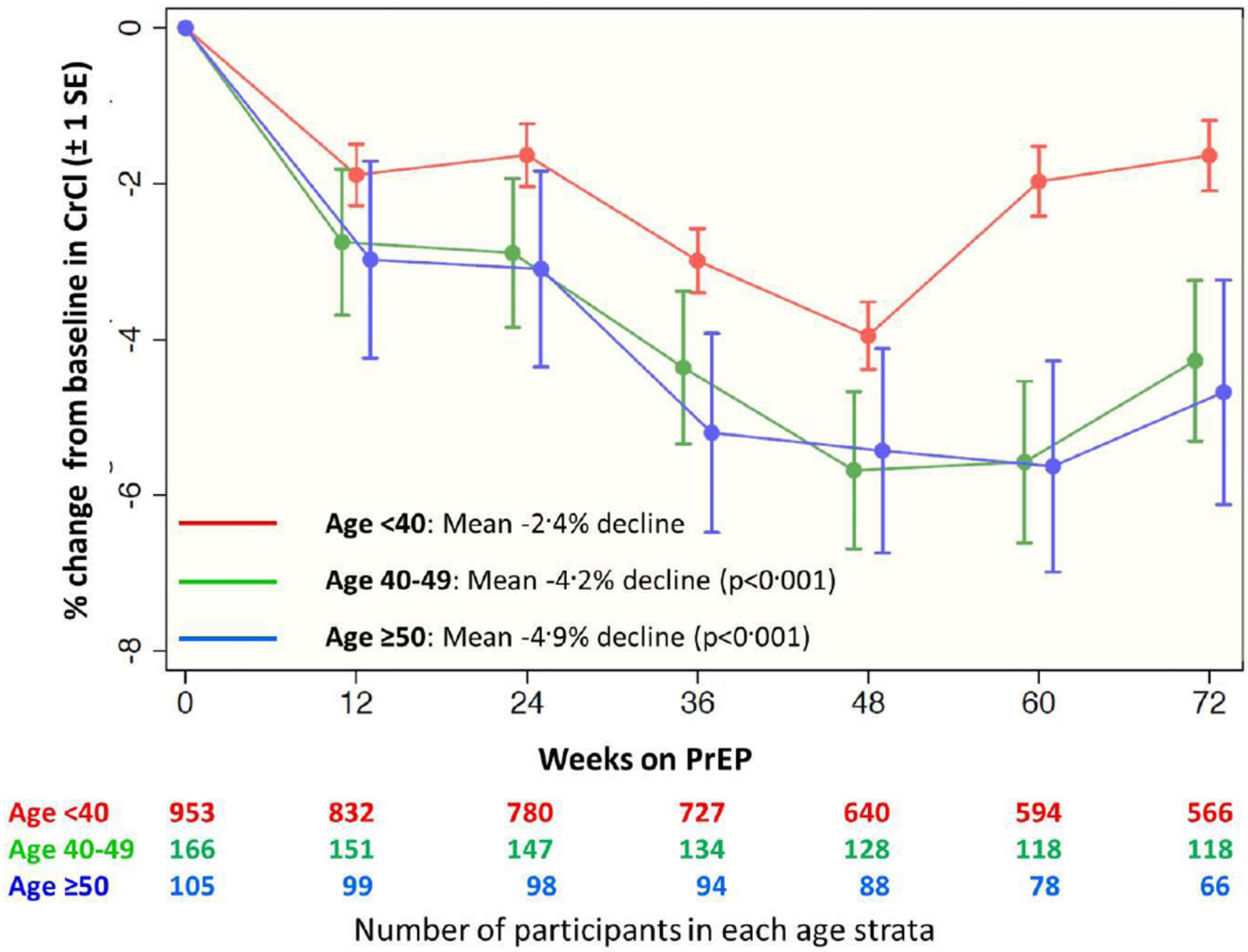

Figure 1.

Change in creatinine clearance over time for iPrEx OLE participants, stratified by baseline age

*Models adjusted for age, baseline CrCl and site of enrollment; p-values compare the % decline in the older age strata to that in those < 40 years; SE – standard error

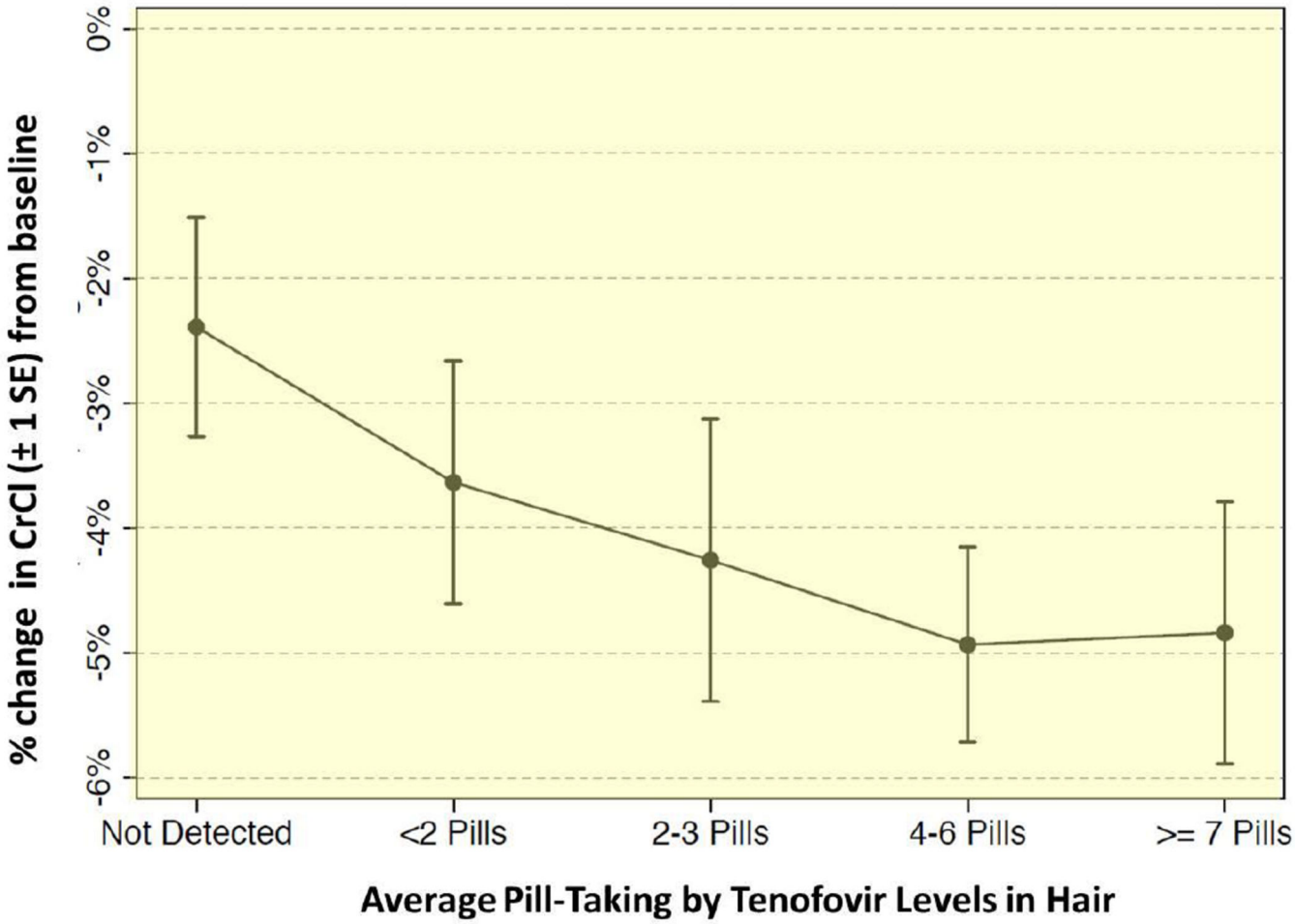

Figure 2.

Relationship between % change in CrCl from baseline and pill taking in iPrEx OLE as determined by hair concentrations

*~ 27% of person-visits had hair levels demonstrating no detectable PrEP use, 16% with <2 pills per week; 9% 2–3 pills per week; 33% 4–6 pills per week; and 16% with daily dosing

Table 1

Baseline characteristics of participants in iPrEx OLE and its hair substudy participants

Characteristic	All iPrEx OLE participants	Hair substudy participants	p-value
Number	1224	220	NA
Person visits contributing to analysis	7475	1114	NA
Age (median, range)	30 (18 – 70)	29 (19 – 70)	0·34
Median time on study (weeks)	72 (71 to 73)	72 (71 to 73)	0·69
Gender identity	1084 (89%) MSM; 140 (11%) transgender women	200 (91%) MSM; 20 (9%) transgender women	0·23
Race/ethnicity	126 (10%) African American 756 (62%) Latino/mixed; 278 (23%) White 64 (5%) Asian	49 (22%) African American; 132 (60%) Latino/mixed; 25 (11%) White; 14 (6%) Asian	0·77
Weight (kg) (mean, SD)	71 (16)	72 (17)	0·19
BMI (kg/m^2) (mean, SD)	24·4 (4·4)	24·6 (4·7)	0·37
Creatinine (mg/dL) (mean, SD)	0·88 (0·14)	0·89 (0·14)	0·42
Creatinine clearance (ml/min) (mean, range)	114 (56 to 208)	114 (63 to 195)	0·56
Visits with hypertension (n, %)	169 (2%)	9 (4%)	0·64
Visits with NSAID use in the prior 30 days (n, %)	1062 (14%)	20 (9%)	0·35
Self-reported adherence (median)	97% overall	97% overall (73% in visits where hair levels demonstrate no detectable PrEP use; 78% in visits with <2 pills per week; 84% in visits with 2–3 pills per week; 89% in visits with 4–6 pills per week; 93% in visits with daily dosing)	0.49
For hair substudy participants only:	**TFV hair concentrations (mean, SD)** 0·027 (0·065) ng/mg **FTC hair concentrations (mean, SD)** 0·45 (0·73) ng/mg		

*SD is standard deviation; Visit with hypertension defined by systolic blood pressure >140mmHg or diastolic blood pressure >90 mmHg; p-values assess differences in characteristics between the two sets of participants

Table 2

Relative risk of participant experiencing creatinine clearance fall to ≤ 70ml/min over the first year on PrEP in the entire iPrEx cohort (Table 2a) and in the hair substudy (Table 2b)

Group	# of visits	% ≥ 1 visit with CrCl falling ≤ 70ml/min over a year on PrEP*	Relative risk	p-value
Table 2a: All iPrEx OLE participants				
Overall	7198	2·6% (1·9 to 3·4%)		
Baseline renal function				
Baseline CrCl ≥ 90 ml/min	6583	0·7% (0·4 to 1·3%)	Ref	
Baseline CrCl < 90 ml/min	615	20·4% (15·1 to 27·2%)	31·2 (16·2 to 60·1)	**<0·001**
Age at initiation of PrEP				
Age <40	5686	0·5% (0·2 to 1·0%)	Ref	
Age 40–50	973	6·4% (3·9 to 10·2%)	13·4 (5·5 to 32·5)	**<0·001**
Age ≥ 50 years	539	16·3% (11·3 to 23·3%)	36·2 (15·6 to 83·9)	**<0·001**
Table 2b: Participants in hair substudy				
Overall	1051	4·5% (2·.6 to 7·7%)		
Baseline renal function				
Baseline CrCl ≥ 90 ml/min	805	1·30%	Reference	
Baseline CrCl < 90 ml/min	146	27·70%	25·4 (6·9 to 93·8)	**<0·001**
Age at initiation of PrEP				
Age <40	940	0·50%	Reference	
Age 40–50	100	12·80%	27·6 (3·2 to 236·0)	**0·002**
Age ≥ 50 years	111	21·30%	48·3 (5·8 to 401·2)	**<0·001**
Drug concentration (TFV or FTC) in hair				
TFV hair level, 1st quartile	298	1·3% (0·2 to 9·1%)	Reference	
TFV hair level, 2nd quartile	266	3·0% (0·7 to 11·3%)	2·2 (0·2 to 24·7)	0·5
TFV hair level, 3rd quartile	252	6·2% (2·4 to 15·6%)	4·7 (0·5 to 42·3)	0·17
TFV hair level, 4th quartile	235	8·2% (3·5 to 18·5%)	6·3 (0·7 to 54·3)	0·092
FTC hair level, 1st quartile	298	1·3% (0·2 to 9·1%)	Reference	

Group	# of visits	% ≥ 1 visit with CrCl falling ≤ 70ml/min over a year on PrEP*	Relative risk	p-value
FTC hair level, 2nd quartile	260	0·0% (0·1 to 1·1%)	0·0 (0·0 to 6·6)	0·263
FTC hair level, 3rd quartile	247	6·3% (2·4 to 15·9%)	4·8 (0·5 to 43·2)	0·159
FTC hair level, 4th quartile	246	10·8% (5·3 to 21·2%)	8·5 (1·0 to 68·9)	**0·046**

*All visits over the duration of the study were used to calculate the rate of falling ≤70ml/min

*The rate of CrCl falling to ≤60 ml/min was low at 0.1% overall in the cohort across all visits (9 of 7198 visits), but all 9 of the drops occurred in participants who started PrEP at CrCl <90ml/min and 8/9 occurred in participants starting PrEP ≥50 years of age (the other participant was 40–49 years old)