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BRIEF REPORT

PrEP Nonadherence, White Coat Dosing, and HIV Risk Among a Cohort of MSM

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Among a cohort of men who have sex with men in a pre-exposure prophylaxis (PrEP) adherence trial, syphilis requiring treatment was associated with white coat dosing (increased PrEP adherence immediately preceding study visits) when compared with participants with optimal drug concentrations. The findings highlight the need for identifying and reducing barriers to PrEP adherence.

Keywords. MSM; pre-exposure prophylaxis; PrEP adherence; syphilis; white coat dosing.

Adherence to prescribed dosing for fixed-dosed daily tenofovir (TFV) disoproxil fumarate and emtricitabine (TDF/FTC)–based HIV pre-exposure prophylaxis (PrEP) is crucial in achieving drug levels that confer protection against HIV seroconversion, with a mean adherence of ≥4 TDF/FTC doses weekly resulting in up to 96%–100% risk reduction of HIV acquisition among men who have sex with men (MSM) [1], [2]. Given the direct correlation of TDF/FTC adherence with PrEP efficacy, HIV prevention trials frequently assess systemic drug concentrations to evaluate adherence to study products and support accurate interpretation of study outcomes [3]. However, perceived expectations from providers or clinic staff may lead individuals to engage in "white coat dosing" (WCD), or increased study product adherence just before a clinic or study visit [4, 5].

While individuals who WCD may have detectable systemic drug levels at the time of assessment, they remain at risk for HIV acquisition, as momentary serum concentrations may be insufficient to confer protection [1, 6]. This consideration is particularly relevant in the context of urine point-of-care assays, which are currently in development to provide real-time assessment of TFV-based PrEP adherence. Urine point-of-care assays rely on short-term TFV concentrations and are not reflective of long-term dosing, leading to potential inaccuracies in the setting of WCD [7–9]. While the phenomenon of WCD has been described in the HIV prevention trial literature, there is a paucity of data explicitly examining WCD within the context of PrEP [10–12]. Given the implications of WCD with regard to HIV acquisition and clinical decision-making, this study seeks to explore factors associated with WCD among a cohort of MSM in Los Angeles who participated in a PrEP adherence trial that provided adjusted adherence support based on TDF/FTC concentrations.

METHODS

Study Population and Design

This is a secondary analysis of MSM enrolled in PATH-PrEP, an open-label study evaluating TDF/FTC PrEP for HIV-uninfected MSM in Los Angeles, California (clinicaltrials.gov #NCT01781806). Detailed methods and results from the study have been published [13]. Briefly, between April 2014 and July 2016, 300 HIV-uninfected MSM were enrolled and assigned to either a PrEP- or postexposure prophylaxis (PEP)–based cohort according to self-reported risk behavior measured against set criteria. Criteria for PrEP cohort assignment included sexual partnership with an HIV-infected individual in the last 4 weeks, sexually transmitted infection (STI; gonorrhea, chlamydia, or syphilis) diagnosis or PEP use in past 12 months, or condomless anal intercourse (CAI) with ≥3 male partners (either HIV-infected or unknown serostatus) in the past 3 months. Participants not meeting PrEP cohort criteria were assigned to the PEP cohort, where risk behaviors were reassessed at follow-up visits, and PrEP cohort "escalation" was offered if risk behaviors met the above-mentioned criteria. This analysis was limited to cisgender MSM, either assigned or escalated to the PrEP cohort, who completed ≥1 follow-up visit. Of the 300 MSM enrolled, 277 were assigned to the PrEP cohort and 23 to the PEP cohort (19 of whom were escalated to PrEP). Of the 296 men assigned or escalated to the PrEP cohort, 281 completed ≥1 follow-up visit and were included in the analysis.

PrEP cohort participants received daily oral TDF/FTC (Truvada, Gilead Sciences, Foster City, CA, USA). Participants were followed for 48 weeks, and those escalated to the PrEP cohort were followed 48 weeks after initiation of PrEP. Study visits occurred at weeks 0, 4, 12, 24, 36, and 48. At each visit, participants completed a computer-assisted self-interview evaluating

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sexual risk behaviors in the past 30 days (CAI with multiple partners, transactional sex, discussion of HIV serostatus before intercourse). At weeks 0, 12, 24, 36, and 48, participants underwent HIV and STI (3 sites for gonorrhea and chlamydia; serologic syphilis) screening, with on-site treatment of prevalent and incident STIs. Adherence to TDF/FTC was assessed by plasma TFV concentrations and dried blood spots (DBS) for TFV-DP and FTC-TP concentrations by liquid chromatography tandem mass spectrometry at weeks 4, 12, 24, 36, and 48 [2, 14]. Plasma TFV concentrations below the lower limit of quantitation (<10 ng/mL) triggered escalated adherence support and outreach.

Patient Consent Statement

All participants underwent written informed consent, and the study protocol was approved by the Office of the Human Research Protection Program (OHRPP) at the University of California, Los Angeles, and the Institutional Review Board of Charles R. Drew University.

Statistical Analysis

Optimal, suboptimal, and WCD concentrations were defined according to drug concentrations consistent with optimal (≥4 doses/week), suboptimal (<4 doses/week), and WCD concentrations at study visits [1, 15]. Optimal and suboptimal concentrations were defined as TFV-DP ≥700 fmol/punch and TFV-DP <700 fmol/punch on DBS, respectively [1, 15]. WCD was defined as TFV-DP <350 fmol/punch on DBS and either or both FTC-TP >0.1 pmol/punch on DBS or plasma TFV >40 ng/mL at the same time point [3, 6, 15]. As plasma TFV concentrations were not obtained at week 48, WCD was defined using only DBS concentrations at this time point (comprising 3 WCD visits). Syphilis requiring treatment was defined as positive rapid plasma reagin (RPR) titer with positive *Treponema pallidum* particle agglutination assay confirmation (if previous titer negative) and/or 4-fold increase in RPR from historical titers. As STI screening did not occur at week 4, STI results from week 0 were carried forward to week 4.

Bivariate analyses were conducted using chi-square testing for categorical predictors and Kruskal-Wallis tests for nonparametric continuous variables. Unadjusted (Supplementary Table 1) and adjusted odds ratios of sexual risk behaviors and syphilis requiring treatment were calculated using mixed-effects generalized structural equation modeling with multinomial logit that compared optimal concentrations with (1) suboptimal concentrations and (2) WCD at study visits. All analyses were conducted using Stata 15.1 (StataCorp, College Town, TX, USA).

RESULTS

Of the 1254 study visits completed by 281 MSM, 73.3% (206/281) completed all 5 study visits, with 89.2% of visits having optimal concentrations (1118/1254), 9.7% suboptimal (122/1254), and 1.1% WCD (14/1254). Among visits with WCD, 64.3% (9/14) had suboptimal concentrations at the study visit immediately preceding WCD. The median participant age (range; SD) was 34 years (20–69; 9.7), and 51.3% (144/281) were white/Caucasian, 9.3% (26/281) black/African American, 27.8% (78/281) Latinx, and 11.7% "other" (33/281). Syphilis requiring treatment was diagnosed at 2.7% (30/1118) of visits with optimal concentrations, 2.5% (3/122) suboptimal, and 14.3% (2/14) WCD ($P = .032$). Transactional sex was reported at 5.2% of visits with optimal concentrations, 11.5% suboptimal, and 7.1% WCD ($P = .019$). Frequency of HIV risk behaviors stratified by PrEP concentrations is shown in Figure 1.

In adjusted analysis, study visits with evidence for WCD had 9.51 times higher odds of syphilis requiring treatment compared with optimal concentrations (95% CI, 1.30–69.38). No differences in syphilis requiring treatment were observed between suboptimal and optimal concentrations. Participants at study visits with suboptimal (aOR, 2.50; 95% CI, 1.40–4.46) and WCD (aOR, 4.85; 95% CI, 1.09–21.60) had higher odds of not discussing HIV serostatus before intercourse, compared with optimal concentrations. No differences were observed in other sexual risk behaviors (CAI with multiple partners, transactional sex) for suboptimal or WCD, when compared with visits with optimal concentrations (Table 1).

DISCUSSION

Among this diverse population of MSM, we found evidence of WCD, though this observation remained rare overall. Individuals who participated in possible WCD demonstrated behavioral and STI-associated risk for HIV acquisition, though confidence intervals were wide due to small sample size. Specifically, participants at visits with suboptimal and WCD concentrations were more likely to report not consistently discussing HIV serostatus before intercourse, compared with visits with optimal drug concentrations. This observation is particularly notable, as these risk behaviors occurred in the context of inadequate prevention-effective drug concentrations, potentially leaving participants vulnerable to HIV acquisition, underscoring the importance of barriers that may impede PrEP adherence in spite of sexual risk behavior [16–19]. Furthermore, these findings highlight the need for increased attention to identifying and reducing these barriers, particularly as HIV acquisition in the setting of inadequate prevention-effective drug concentrations may select for resistant viral quasispecies should seroconversion occur [20].

It is possible that individuals who engaged in WCD were influenced by social desirability perception, as approximately two-thirds of participants had suboptimal concentrations at study visits immediately preceding WCD. These findings suggest that participants may have been motivated to engage in WCD to gain approval (or avoid disapproval) of the study team, particularly as

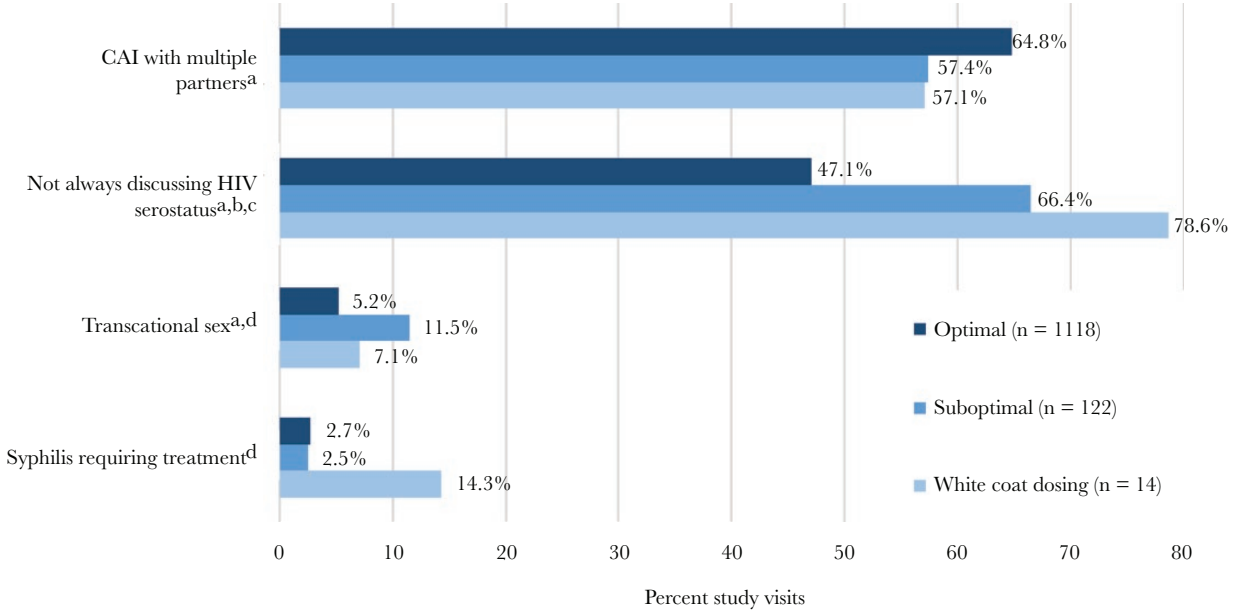

Figure 1. Frequency of HIV risk behaviors and syphilis requiring treatment with optimal, suboptimal, and white coat dosing concentrations at study visits among a cohort of men who have sex with men using PrEP (n = 1254). Syphilis was screened at each study visit and defined as a positive RPR titer with positive TPPA confirmation (if previous titer negative) and/or 4-fold increase in RPR from historical titers. [a]Last 30 days. [b]Before intercourse. [c]$P \leq .001$. [d]$P \leq .05$. Abbreviations: CAI, condomless anal intercourse; PrEP, pre-exposure prophylaxis; RPR, rapid plasma regain; TPPA, *Treponema pallidum* particle agglutination assay.

Table 1. Adjusted Odds Ratios of Factors Associated With Suboptimal Drug Concentrations and White Coat Dosing Among a Cohort of Men who Have Sex With Men Using PrEP[a]

	Suboptimal		White Coat Dosing	
	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age	0.95 (0.91–0.98)	**.007**	0.98 (0.91–1.06)	.66
Race/ethnicity				
White/Caucasian	Ref	—	Ref	—
Black/African American	5.88 (1.87–18.46)	**.002**	5.75 (0.72–46.09)	.1
Latinx	0.92 (0.37–2.25)	.85	0.68 (0.10–4.57)	.69
Other	0.72 (0.21–2.43)	.59	0.62 (0.04–9.03)	.72
CAI[b] with multiple partners[c]				
No	Ref	—	Ref	—
Yes	0.72 (0.41–1.28)	.27	0.79 (0.22–2.90)	.72
Transactional sex[c]				
No	Ref	—	Ref	—
Yes	2.46 (0.79–7.69)	.12	2.16 (0.17–27.23)	.55
Syphilis requiring treatment[d]				
No	Ref	—	Ref	—
Yes	1.00 (0.23–4.37)	1.00	9.51 (1.30–69.38)	**.026**
Discussed HIV serostatus[ce]				
Always	Ref	—	Ref	—
Not always	2.50 (1.40–4.46)	**.002**	4.85 (1.09–21.60)	**.039**

Abbreviations: CAI, condomless anal intercourse; OR, odds ratio; PrEP, pre-exposure prophylaxis; RPR, rapid plasma regain; TPPA, *Treponema pallidum* particle agglutination assay.

[a]Calculated using mixed-effects generalized structural equation model with multinomal logit comparing optimal with (1) suboptimal concentrations and (2) white coat dosing at study visits, controlling for all predictors listed in table.

[b]Condomless anal intercourse.

[c]Last 30 days.

[d]Syphilis was screened at each study visit and defined as positive RPR titer with positive TPPA confirmation (if previous titer negative) and/or 4-fold increase in RPR from historical titers.

[e]Before intercourse; *P* values <.05 in bold.

this was a PrEP adherence trial [21–23]. Despite this, visits with evidence for WCD had higher odds of syphilis requiring treatment compared with visits with optimal drug concentrations, though the confidence intervals were wide. However, no differences in syphilis requiring treatment were observed between visits with suboptimal and optimal drug concentrations, suggesting that individuals who WCD may be at higher risk for HIV seroconversion, given known associations between syphilis and HIV acquisition [24]. These findings underscore the importance of support that minimizes social desirability bias while navigating potential barriers to PrEP adherence in the setting of WCD.

Our study has several strengths. Data were collected as part of a longitudinal study with high retention rates and well-curated objective assessments of adherence using multiple platforms. Limitations include that the number of WCD study visits was small, limiting power to detect associations. However, we anticipate that this phenomenon will be encountered more frequently with the development and uptake of point-of-care drug monitoring assays [8, 25]—emphasizing the importance of exploring factors associated with WCD within the context of PrEP and the need for larger studies to confirm our findings. Finally, as our analysis was limited to cis-gender MSM, these findings may not be generalizable to transgender populations. Given the unique barriers to PrEP experienced by these populations, this is an important area of future study. In conclusion, participants at study visits with WCD demonstrated increased behavioral and biological risk for HIV acquisition—revealing a precarious clinical scenario in which HIV protection may be limited and stressing the importance of increased support for PrEP adherence among these individuals.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. R.J.L. has received consulting fees and travel support from Gilead Sciences and Merck, Inc., as well as honoraria from Roche. R.H.H. is an employee of Gilead. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. R.J.L. and C.S.B. devised the project and analysis. R.K.B., W.C.J., and A.R.W. collected data. C.S.B., M.R.B., R.M.K., and R.J.L. analyzed results. All authors provided critical feedback on all manuscript drafts and approved the final manuscript.

References

1. Anderson PL, Glidden DV, Liu A, et al; iPrEx Study Team. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med **2012**; 4:151ra125.
2. Grant RM, Anderson PL, McMahan V, et al; iPrEx study team. 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**; 14:820–9.
3. Castillo-Mancilla JR, Haberer JE. Adherence measurements in HIV: new advancements in pharmacologic methods and real-time monitoring. Curr HIV/AIDS Rep **2018**; 15:49–59.
4. Feinstein AR. On white-coat effects and the electronic monitoring of compliance. Arch Intern Med **1990**; 150:1377–8.
5. Podsadecki TJ, Vrijens BC, Tousset EP, et al. "White coat compliance" limits the reliability of therapeutic drug monitoring in HIV-1-infected patients. HIV Clin Trials **2008**; 9:238–46.
6. Castillo-Mancilla J, Seifert S, Campbell K, et al. Emtricitabine-triphosphate in dried blood spots as a marker of recent dosing. Antimicrob Agents Chemother **2016**; 60:6692–7.
7. Anderson PL. What can urine tell us about medication adherence? EClinicalMedicine **2018**; 2–3:5–6.
8. Gandhi M, Bacchetti P, Spinelli MA, et al. Brief report: validation of a urine tenofovir immunoassay for adherence monitoring to PrEP and ART and establishing the cutoff for a point-of-care test. J Acquir Immune Defic Syndr **2019**; 81:72–7.
9. Spinelli MA, Rodrigues W, Wang G, et al. Near-perfect accuracy of a real-time urine tenofovir test compared to lab-based ELISA. Paper presented at: Conference on Retroviruses and Opportunistic Infections; March 10, 2020; Boston, MA.
10. Corneli AL, Deese J, Wang M, et al; FEM-PrEP Study Group. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. J Acquir Immune Defic Syndr **2014**; 66:324–31.
11. van der Straten A, Montgomery ET, Musara P, et al; Microbicide Trials Network-003D Study Team. Disclosure of pharmacokinetic drug results to understand nonadherence. AIDS **2015**; 29:2161–71.
12. Phillips TK, Sinxadi P, Abrams EJ, et al. A Comparison of plasma efavirenz and tenofovir, dried blood spot tenofovir-diphosphate, and self-reported adherence to predict virologic suppression among South African women. J Acquir Immune Defic Syndr **2019**; 81:311–8.
13. Landovitz RJ, Beymer M, Kofron R, et al. Plasma tenofovir levels to support adherence to TDF/FTC preexposure prophylaxis for HIV prevention in MSM in Los Angeles, California. J Acquir Immune Defic Syndr **2017**; 76:501–11.
14. Grant RM, Lama JR, Anderson PL, et al; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med **2010**; 363:2587–99.
15. 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 Res Hum Retroviruses **2013**; 29:384–90.
16. Pasipanodya EC, Jain S, Sun X, et al; California Collaborative Treatment Group (CCTG) TAPIR Study Team. Trajectories and predictors of longitudinal preexposure prophylaxis adherence among men who have sex with men. J Infect Dis **2018**; 218:1551–9.
17. Myers JJ, Kang Dufour MS, Koester KA, et al. Adherence to PrEP among young men who have sex with men participating in a sexual health services demonstration project in Alameda county, California. J Acquir Immune Defic Syndr **2019**; 81:406–13.
18. Goodman-Meza D, Beymer MR, Kofron RM, et al. Effective use of pre-exposure prophylaxis (PrEP) among stimulant users with multiple condomless sex partners: a longitudinal study of men who have sex with men in Los Angeles. AIDS Care **2019**; 31:1228–33.
19. Wood S, Gross R, Shea JA, et al. Barriers and facilitators of PrEP adherence for young men and transgender women of color. AIDS Behav **2019**; 23:2719–29.
20. Parikh UM, Mellors JW. Should we fear resistance from tenofovir/emtricitabine preexposure prophylaxis? Curr Opin HIV AIDS **2016**; 11:49–55.
21. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med **2015**; 5:470–82.
22. Driscoll KA, Wang Y, Johnson SB, et al. White coat adherence occurs in adolescents with type 1 diabetes receiving intervention to improve insulin pump adherence behaviors. J Diabetes Sci Technol **2017**; 11:455–60.
23. Modi AC, Ingerski LM, Rausch JR, et al. White coat adherence over the first year of therapy in pediatric epilepsy. J Pediatr **2012**; 161:695–9.e1.
24. Kidd S, Torrone E, Su J, Weinstock H. Reported primary and secondary syphilis cases in the United States: implications for HIV infection. Sex Transm Dis **2018**; 45:42–7.
25. Koss CA, Bacchetti P, Hillier SL, et al. Differences in cumulative exposure and adherence to tenofovir in the VOICE, iPrEx OLE, and PrEP demo studies as determined via hair concentrations. AIDS Res Hum Retroviruses **2017**; 33:778–83.