Discrepancies Between Self-Reported Adherence and a Biomarker of Adherence in Real-World Settings

Shane Hebel, JD,[a] Elijah Kahn-Woods, BS,[a] Sheryl Malone-Thomas, DNP, RN, FNP-BC,[b] Marlene McNeese, BS,[b] Lupita Thornton, BS,[b] Adam Sukhija-Cohen, PhD, MPH,[c] Henna Patani, BDS, MPH,[c] Whitney Engeran, BS,[c] and Giffin Daughtridge, MD, MPA[a]

Background: Pre-exposure prophylaxis (PrEP) is only effective in preventing new HIV infections when taken consistently. In clinical practice, asking a patient about their adherence (self-report) is the predominant method of assessing adherence to PrEP. Although inexpensive and noninvasive, self-report is subject to social desirability and recall biases. Several clinical trials demonstrate a discrepancy between self-reported adherence and biomarker-based recent adherence. Less is known about the accuracy of self-report in real-world clinical settings. This brief report addresses this knowledge gap and describes the concordance between self-reported adherence and biomarker-based adherence in real-world clinical settings.

Methods: A liquid chromatography–mass spectrometry urine test for tenofovir was developed and used clinically to detect recent nonadherence (no dose in at least 48 hours) for each individual. Two clinics' standard operating procedures recommend utilization of the urine-based adherence test for patients who self-report that they are not struggling with adherence. Those who self-report struggling with adherence receive enhanced adherence support without the need for additional testing. The number of results indicating recent nonadherence from these 2 clinics were analyzed to assess the concordance between self-reported adherence and biomarker-based adherence.

Results: Across 2 clinics, 3987 tests were conducted from patients self-reporting as "adherent," and 564 [14.1%; 95% confidence interval (CI): 13.1% to 15.2%] demonstrated recent nonadherence with the liquid chromatography–mass spectrometry test. At clinic #1 in Florida, 3200 tests were conducted, and 465 (14.5%; 95% CI: 13.3% to 15.8%) demonstrated recent nonadherence. At clinic #2 in Texas, 787 tests were conducted, and 99 (12.6%; 95% CI: 10.4% to 14.9%) demonstrated recent nonadherence.

Conclusions: Utilization of biomarker-based adherence monitoring at these 2 clinics resulted in 564 additional patients receiving enhanced adherence support who otherwise would not have been identified as nonadherent to their prescribed PrEP regimen. These findings suggest that objective adherence monitoring can be used clinically to enable providers to identify nonadherent patients and allocate support services accordingly.

Key Words: PrEP, tenofovir, adherence, self-report

(*J Acquir Immune Defic Syndr* 2020;85:454–457)

INTRODUCTION

Pre-exposure prophylaxis (PrEP) with once daily tenofovir disoproxil fumarate/emtricitabine has demonstrated consistently high efficacy in reducing the risk of HIV infection among those at risk of HIV acquisition.[1–6] High adherence to PrEP is associated with greater risk reduction, and suboptimal adherence is shown to reduce PrEP efficacy.[2,3,7–9] The United States Preventive Services Task Force recommends with Grade A certainty that clinicians offer PrEP to those at risk of HIV acquisition and notes that there is "convincing evidence that adherence to PrEP is highly correlated with its efficacy."[10]

Because the US Department of Health and Human Services strives to reduce the number of new HIV infections in the United States by 75% in the next 5 years and by 90% in the next 10 years under the *Ending the HIV Epidemic: A Plan for America* initiative, scaling access to PrEP is an explicit national public health priority.[11] Adherence to PrEP will largely determine the effectiveness of *Ending the HIV Epidemic* and suboptimal adherence will undermine efforts and investments in extending PrEP access to those at highest risk. Accordingly, it is increasingly critical that clinicians are able to accurately assess PrEP adherence in clinical settings to support patients in remaining protected from HIV acquisition.

In clinical practice, asking a patient about their adherence ("self-report") is the predominant method of assessing adherence to PrEP. Self-report is inexpensive, noninvasive, and provides rapid results, thus permitting its widespread implementation in clinical settings. However, this subjective method of assessing adherence is subject to social desirability or recall biases, and many PrEP clinical trials have noted an overestimation of self-reported adherence.[12–16] Conversely, some studies have found a closer correlation between self-report and biomarker-based, objective adherence; differences in how adherence questions are posed to patients may influence the accuracy of the response.[17,18]

Received for publication March 31, 2020; accepted August 13, 2020.

From the [a]UrSure, Inc., Boston, MA; [b]Houston Health Department, Houston, TX; and [c]AIDS Healthcare Foundation, Public Health Division, Los Angeles, CA.

G.D., S.H., and E. K-W. are paid employees of UrSure, Inc. The remaining authors have no conflicts of interest to declare.

Correspondence to: Giffin Daughtridge, MD, MPA, Harvard Life Lab Attn: UrSure, Inc., 127 Western Ave Boston, MA 02134 (e-mail: giffin@ursureinc.com).

TABLE 1. Baseline Characteristics of Patients Self-Reporting as "Adherent" at 2 Clinics in Broward County, FL, and Houston, TX

Characteristic	Total (n = 1520) (%)	Clinic #1 (n = 1265) (%)	Clinic #2 (n = 255) (%)
Age			
≤20	65 (4.3)	51 (4.0)	14 (5.5)
21–30	607 (39.9)	494 (39.1)	113 (44.3)
31–40	435 (28.6)	353 (27.9)	82 (32.2)
41–50	207 (13.6)	177 (14.0)	30 (11.8)
51–60	138 (9.1)	125 (9.9)	13 (5.1)
>60	65 (4.3)	62 (4.9)	3 (1.2)
Not specified	3 (0)	3 (0.2)	0 (0)
Sex assigned at birth			
Male	1340 (88.2)	1131 (89.4)	209 (82.0)
Female	118 (8.1)	90 (7.1)	28 (11.0)
Not specified	62 (4.1)	44 (3.5)	18 (7.1)
Gender			
Cisgender male	1317 (86.6)	1129 (89.2)	188 (73.7)
Cisgender female	98 (6.4)	71 (5.6)	27 (10.6)
Assigned male at birth—female	12 (0.8)	12 (0.9)	0 (0)
Assigned female at birth—male	5 (0.3)	4 (0.3)	1 (0.4)
Other	2 (0.1)	2 (0.2)	0 (0)
Not specified	86 (5.7)	47 (3.7)	39 (15.3)
Sexual orientation			
Homosexual	1120 (73.7)	952 (75.3)	168 (65.9)
Bisexual	140 (9.2)	130 (10.3)	10 (3.9)
Heterosexual	158 (10.4)	121 (9.6)	37 (14.5)
Other	1 (0.1)	1 (0.1)	0 (0)
Not specified	101 (6.6)	61 (4.8)	40 (15.7)
Race			
African American	334 (22.0)	260 (20.6)	74 (29.0)
American Indian/Native Alaskan	8 (0.5)	8 (0.6)	0 (0)
Asian	43 (2.8)	35 (2.8)	8 (3.1)
Native Hawaiians/Other Pacific Islanders	2 (0.1)	2 (0.2)	0
White	952 (62.6)	818 (64.7)	134 (52.5)
Not specified	181 (11.9)	142 (11.2)	39 (15.3)
Ethnicity			
Hispanic-Latino	665 (43.8)	543 (42.9)	122 (47.8)
Non-Hispanic/Latino	746 (49.1)	653 (51.6)	93 (36.5)
Not specified	109 (7.2)	69 (5.5)	40 (15.7)

The use of biomarkers to measure drug concentrations in various matrices (eg., blood, urine, and hair) enable objective quantification of adherence to PrEP. Several biomarker-based objective adherence monitoring (OAM) methods have been developed and used in research settings to assess PrEP adherence. Plasma-based, dried blood spot–based, and hair-based adherence monitoring tools require access to specialized laboratory equipment and personnel. This can be expensive and time-intensive, thereby limiting the potential for clinical application.

A liquid chromatography tandem–mass spectrometry (LC-MS/MS) urine test for tenofovir (TFV) is presently the only commercialized, biomarker-based method of objectively assessing adherence to PrEP. The LC-MS/MS test has demonstrated that it can reliably measure TFV concentration in urine over the preceding 48 hours with high sensitivity and specificity, and that urine TFV concentrations correlate with other biomarker-based OAM methods.[24] Urine-based OAM has been found to be noninvasive, acceptable to patients, and feasible to implement.[19] Urine TFV adherence testing using the external LC-MS/MS has been introduced into the standard of care at >25 clinics nationwide. Two such clinics' standard operating procedures recommend utilization of the urine-based adherence test for patients who self-report that they are not struggling with adherence, as those who self-report nonadherence automatically receive enhanced adherence support without the need for additional testing. The number of results indicating recent nonadherence from these 2 clinics were collected and analyzed to assess the concordance of self-reported adherence to biomarker-based adherence, as measured with an objective urine biomarker. This brief report strives to add to the above-mentioned literature from clinical trials to depict the discrepancy between self-reported adherence and biomarker-based adherence in real-world clinical settings.

METHODS

Urine samples for LC-MS/MS TFV testing were collected from PrEP patients at 2 clinics whose standard operating procedures reserve urine adherence testing for those who self-report as adherent. Clinic #1 is a nonprofit health center based in Broward County, Florida, that provides comprehensive sexually transmitted infection and HIV/AIDS care to patients in one of the regions with the highest burden of HIV in the country. Clinic #2 is an urban department of health in Houston, Texas, that provides comprehensive sexual health services to patients.

Urine samples were collected from all individuals as part of routine sexually transmitted infection testing but only sent for LC-MS/MS for patients who self-reported as "adherent." Adherence test results were reported back to providers in 3–5 days and individuals identified as nonadherent with the LC-MS/MS test received enhanced adherence support, per clinics' standard operating procedures.

From October 2018 to May 2020, patients presented to the clinics for routine quarterly PrEP visits. Urine samples were collected from all individuals as part of routine sexually transmitted infection testing. Patients were asked about their recent PrEP pill taking habits and providers interpreted these responses as either "adherent" or "non-adherent." Providers determined this based on their clinical experience. Typically, if an individual would be classified as adherent unless they specifically mentioned that they had missed >1 dose in the previous week or specifically indicated that they were struggling with adherence. For patients who self-reported as "adherent," a portion of their urine sample was aliquoted and sent to an external laboratory for adherence testing with the LC-MS/MS urine TFV test. The LC-MS/MS urine TFV test identified individuals who had not taken the drug in at least the previous 48 hours. Adherence support services were extended to patients who self-reported as nonadherent and those whose LC-MS/MS test result indicated they had not recently taken a dose of PrEP. Adherence data were aggregated and retrospectively analyzed to assess the concordance of self-reported adherence and biomarker-based recent adherence, as defined by the objective LC-MS/MS urine TFV test.

Per standard operating procedures, all patients who received urine adherence testing were, by definition, categorized as having self-reported recent adherence. The number of patients identified as recently nonadherent with the LC-MS/MS test was subtracted from the number of total number of patients receiving urine adherence testing to calculate the discrepancy between self-reported adherence and biomarker-based recent adherence. Biomarker-based recent nonadherence proportion was calculated by dividing the number of samples indicating recent nonadherence over the total number of samples collected. Ninety-five percent confidence intervals (CIs) were calculated for each nonadherence proportion.

RESULTS

Across the 2 clinics, 3987 tests were conducted from 1520 unique patients self-reporting as "adherent." Across all patients, 88.2% were sex assigned at birth as men, 7.8% were sex assigned at birth as women, and the median age was 32 years (range: 18–83 years). Baseline characteristics for all patients who received at least one adherence test are described in Table 1.

In total, 564 (14.1%; 95% CI: 13.1% to 15.2%) LC-MS/MS test results indicated recent nonadherence (Fig. 1). At clinic #1, 3200 tests were conducted, and 465 (14.5%; 95% CI: 13.3% to 15.8%) LC-MS/MS results indicated recent nonadherence. At clinic #2, 787 tests were conducted, and 99 (12.6%; 95% CI: 10.4% to 14.9%) LC-MS/MS results indicated recent nonadherence.

DISCUSSION

Results from the routine use of urine-based OAM at these 2 clinics demonstrate that there is a discordance between self-reported adherence and biomarker-based recent adherence in real-world, clinical settings. Utilization of urine-based OAM at these 2 clinics resulted in 564 additional patients being offered enhanced adherence support who otherwise would not have been identified as not having HIV protection from PrEP. These findings suggest that OAM methods could be used clinically to enable providers to identify nonadherent patients who are not currently being identified by self-report and allocate support services accordingly.

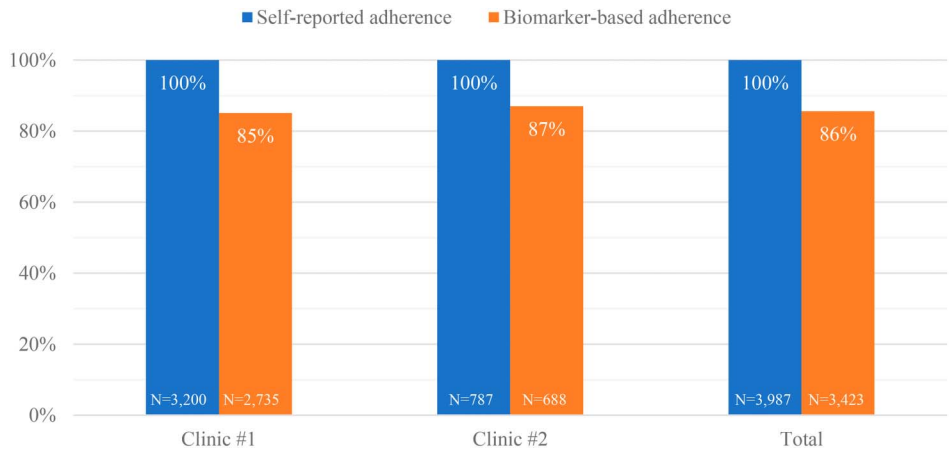

FIGURE 1. Self-reported and biomarker-based PrEP adherence. full color online

Although the accuracy of self-report may vary by demographic or subpopulation, one study suggests that younger patients and African American patients are more likely to overestimate PrEP adherence than their counterparts.[13] This is especially concerning considering that young people, African Americans, and Latinos present higher HIV incidence and PrEP nonadherence rates than their counterparts.[20,21] The inaccuracy of self-report, especially among vulnerable patients, is likely driven by complex historical and social factors, including systemic discrimination, stigma, and distrust of the medical system.[22,23] Conversely, anecdotal evidence from providers at these 2 clinics tentatively suggests OAM can help alleviate this distrust by inciting opportunities to openly, objectively discuss barriers to adherence, thereby strengthening the patient–provider relationship and reducing subjectivity or bias from the conversation.

The strength of this study is derived from the simplicity of its design, as the standard operating procedures at these clinics enable clear comparison of self-reported and objective, biomarker-based adherence in real-world clinical settings. This novel implementation science data aligns with the above-mentioned findings from clinical trial settings in depicting a discrepancy between self-reported adherence and biomarker-based adherence.

This study design faces several limitations. First, because adherence tests are only conducted for patients who self-report as adherent, less is known about the adherence patterns of patients who self-report as nonadherent. This precludes assessment of the accuracy of self-reported adherence by demographics. Second, urine TFV testing is a short-term measure of adherence and is subject to "white coat adherence," whereby an individual is nonadherent but takes a dose the day of their appointment. Individuals who did this would not have been identified as nonadherent in this analysis; therefore, it is possible that the discordance between self-report and biomarker-based adherence is even greater than what is depicted here. Finally, because this study is retrospective and did not use a questionnaire to assess self-reported adherence, variances in how clinicians posed their self-report question and how they interpreted results may have influenced study results.

For United States Preventive Services Task Force and Health and Human Service to accomplish the ambitious goals stated under *Ending the HIV Epidemic*, providers will need to be able to accurately assess adherence to PrEP, especially for the most vulnerable subpopulations. Although self-reported adherence may be inexpensive and easy to conduct, its inaccuracy threatens to dilute the impact of gains in PrEP uptake. Policymakers can safeguard their investments in PrEP uptake by considering policies and guidelines that optimize PrEP scale-up efforts and ensure that PrEP works effectively for those who need it most.

REFERENCES

1. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet.* 2016;387:53–60.
2. Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. *JAMA Intern Med.* 2016;176:75.
3. 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; 14:820–829.
4. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med.* 2012;367:423–434.
5. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med.* 2012;367: 399–410.
6. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med.* 2010; 363:2587–2599.
7. Hojilla JC, Vlahov D, Glidden DV, et al. Skating on thin ice: stimulant use and sub-optimal adherence to HIV pre-exposure prophylaxis. *J Int AIDS Soc.* 2018;21:e25103.
8. Desai M, Field N, Grant R, et al. Recent advances in pre-exposure prophylaxis for HIV. *BMJ.* 2017;359:j5011.
9. 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;4:151ra125.
10. Owens DK, Davidson KW, Krist AH, et al. Preexposure prophylaxis for the prevention of HIV infection. *JAMA.* 2019;321:2203.
11. US Department of Health & Human Services. *Ready, Set, PrEP Expands Access to Medication to Prevent HIV*. Washington, DC: HHS Press Office; 2019.
12. Gorbach PM, Mensch BS, Husnik M, et al. Effect of computer-assisted interviewing on self-reported sexual behavior data in a microbicide clinical trial. *AIDS Behav.* 2013;17:790–800.
13. Baker Z, Javanbakht M, Mierzwa S, et al. Predictors of over-reporting HIV pre-exposure prophylaxis (PrEP) adherence among young men who have sex with men (YMSM) in self-reported versus biomarker data. *AIDS Behav.* 2018;22:1174–1183.
14. van der Straten A, Brown ER, Marrazzo JM, et al. Divergent adherence estimates with pharmacokinetic and behavioural measures in the MTN-003 (VOICE) study. *J Int AIDS Soc.* 2016;19:20642.
15. Musinguzi N, Muganzi CD, Boum Y, et al. Comparison of subjective and objective adherence measures for preexposure prophylaxis against HIV infection among serodiscordant couples in East Africa. *AIDS.* 2016; 30:1121–1129.
16. Amico KR, Marcus JL, McMahan V, et al. Study product adherence measurement in the iprex placebo-controlled trial. *J Acquir Immune Defic Syndr.* 2014;66:530–537.
17. Haberer JE. Current concepts for PrEP adherence in the PrEP revolution. *Curr Opin HIV AIDS.* 2016;11:10–17.
18. Blumenthal J, Pasipanodya EC, Jain S, et al. Comparing self-report pre-exposure prophylaxis Adherence questions to pharmacologic measures of recent and cumulative pre-exposure prophylaxis exposure. *Front Pharmacol.* 2019;10:721.
19. Hunt T, Lalley-Chareczko L, Daughtridge G, et al. Challenges to PrEP use and perceptions of urine tenofovir adherence monitoring reported by individuals on PrEP. *AIDS Care.* 2019;31:1203–1206.
20. Hess KL, Hu X, Lansky A, et al. Lifetime risk of a diagnosis of HIV infection in the United States. *Ann Epidemiol.* 2017;27:238–243.
21. Johnson S, Dailey A, Johnson AS, et al. *Diagnoses of HIV Infection in the United States and Dependent Areas (Preliminary) HIV Surveillance Supplemental Report 2 Vol. 30*. 2018. Available at: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html, http://wwwn.cdc.gov/dcs/ContactUs/Form. Accessed March 24, 2020.
22. Corbie-Smith G, Thomas SB, st. George DMM. Distrust, race, and research. *Arch Intern Med.* 2002;162:2458.
23. Kennedy BR, Mathis CC, Woods AK. African Americans and their distrust of the health care system: healthcare for diverse populations. *J Cult Divers.* 2007;14:56–60.
24. Koenig HC, Mounzer K, Daughtridge GW, et al. Urine assay for tenofovir to monitor adherence in real time to tenofovir disoproxil fumarate/emtricitabine as pre-exposure prophylaxis. *HIV Med.* 2017;18:412–418.