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Physician Estimate of Antiretroviral Adherence in India: Poor Correlation with Patient Self-Report and Viral Load

L. Walshe, B.S.N., M.P.H.,[1] D.G. Saple, M.D.,[2] S.H. Mehta, Ph.D., M.P.H.,[1] B. Shah, M.D.,[3] R.C. Bollinger, M.D., M.P.H.,[1,4] and A. Gupta, M.D., M.H.S.[4]

Abstract

Adherence to antiretroviral therapy (ART) is critical in maintaining viral suppression and minimizing resistance in HIV-infected patients. We compared physician estimates of their patients' ART adherence with participant's self-reported adherence to determine patient-provider agreement and identify correlates of discordance in three private clinics in Mumbai, India. Between December 2004 and April 2005, 277 persons receiving ART at three private clinics in Mumbai, India, were interviewed regarding adherence to ART using the Adult AIDS Clinical Trials Group questionnaire. Physicians were also asked to assess their patients' adherence. Quantitative HIV-1 RNA level was determined for 200 participants. Agreement between provider estimate of adherence and participant self-report was low, $\kappa = 0.058$ (95% confidence interval [CI] 0.011–0126). Of 200 participants whose viral load was obtained, viral suppression was associated with participant self-reported adherence (odds ratio [OR] 3.08; 95% CI 1.65–5.74; $p < 0.05$), but not with provider estimated adherence (OR 1.2; 95% CI 0.67-2.14; $p = 0.54$). Cost of ART was positively associated with physician underestimation of participant adherence and older age was negatively associated. No independent correlates of physician overestimation of participant adherence were found. There was poor agreement between physician estimate of adherence and patient self-report. Providers should avoid using their own assessment of patient ART adherence. Instead, providers should rely on effective and validated measures, especially when viral load or drug level monitoring are not readily available.

Introduction

The World Health Organization (WHO) reports that of the estimated 2.5 million HIV-positive people in India,[1] 785,000 are in need of antiretroviral therapy (ART). The government's National AIDS Control Organization program aims to provide ART to 300,000 adults and 40,000 children over 6 years by 2011.[2] A significant and increasing number of HIV-infected persons are also seeking ART treatment in the private sector,[2] where decreasing drug costs allow for greater ART access.

Appropriate combinations of ART significantly reduce HIV morbidity and mortality.[3,4] However, suboptimal adherence to ART regimens is associated with virologic failure,[5–7] drug resistance, and disease progression. A provider estimate of adherence is an inexpensive measure, however, research to date suggests providers are poor at estimating adherence in non-HIV–[8] and HIV-infected patients.[5,9,10] While patient self-report has been shown to overestimate adherence, structured self-report has in some cases correlated well with clinical measures of adherence.[6,7,11–13]

In India, both public and private sector HIV clinics often have large numbers of patients (with individual providers often seeing more than 100 patients per day), with little time to assess and counsel patients. Furthermore, physicians often use their own judgment to assess patient adherence to medications. However, little data exist specific to the Indian setting regarding physician estimate of adherence. Our objective was to compare physician estimates of their patients ART adherence with participant self-reported adherence to determine patient–provider agreement and identify correlates of discordance, in three private clinics in Mumbai, India.

Methods

We conducted a cross-sectional study among 277 HIV-infected patients receiving ART in three private outpatient clinics in Mumbai from December 2004 through April 2005.

[1]Bloomberg School of Public Health, [4]School of Medicine, Johns Hopkins University, Baltimore, Maryland.
[2]Human Healthcare and Research Foundation, Mumbai, India.
[3]Department of Emergency Medicine, School of Medicine, Emory University, Atlanta, Georgia.

A random sample of 200 of the 277 participants was chosen to undergo virologic testing. The study design and methods have been previously described.[14] The study was approved by the Johns Hopkins School of Medicine Institutional Review Board and a local Mumbai ethics committee and all participants provided written informed consent

Clinic sites and provider characteristics

Clinic sites were located in three geographically distinct areas of Mumbai – central (Dadar), northern (Malad), and eastern (Ulhasanagar). A convenience sample of three clinics was chosen based on total numbers of patients receiving ART at these clinics and available resources. A physician and an assistant staffed each clinic site. Each physician had a local reputation for treating HIV patients and prescribing ART. The size of practice varied from 150–2500 HIV patients, with an estimated 14%–60% of patients on ART. The physicians had 6–16 years of HIV experience.

Data collection

The participant's physician completed a 16-question provider survey on the same day as the participant's interview and both surveys are previously described.[14] Providers were asked to estimate their patients' adherence as ≥95%, between 70% and 95%, or less than 70%. At the time of the survey, patient viral load information was generally not available to providers. Viral load tests were drawn on the same day as the surveys were completed.

Each participant completed a face-to-face 45-minute, 145-question administered survey regarding HIV care and ART adherence. Participant adherence was assessed using the validated Adult AIDS Clinical Trials Group (AACTG) questionnaire, responses to which have been shown to correlate with plasma viremia.[6,14] Adherence was defined as having taken 95% or more of the prescribed doses over the past 4 days. To mitigate participant concerns regarding disclosure of nonadherence, we followed suggestions made by Chesney et al.,[15] including having a trained interviewer and a preamble before the adherence questions to state the participant was not being judged, honest answers were being sought, and no answers would be shared with their physician.

Laboratory assessment

Quantitative HIV-1 RNA levels were assessed using the Amplicor Monitor Standard Assay, version 1.5 (Roche Molecular Systems, Alameda, CA), which is validated for subtype C. Detection limit of 400 copies per milliliter was used for HIV-RNA measurement and those with a viral load less than 400 copies per milliliter were defined as virologically suppressed.

Statistical methods

Validity of physician estimates of adherence was assessed by calculating sensitivity, specificity, positive and negative predictive value, treating the patient adherence report as the gold standard. Agreement (reliability), between the physician estimate and the patient self-report, was assessed by calculating a weighted κ statistic and corresponding 95% confidence interval (at levels <70%, ≥70%– <95%, and ≥95%). We further assessed correlates of discordance (with respect to ≥95% adherence) between these two measurements. Three main groups were defined: (1) concordance: defined as both physician and patient self-report at either ≥95% or <95%; (2) underestimation: defined as physician assessment of <95% adherence and patient self-report of ≥95% adherence; and 3) overestimation: defined as physician assessment of ≥95% adherence and patient self-report of <95% adherence. Formal assessment of factors associated with each of these three groups was performed using univariate analysis and multivariate multinomial logistic regression. In these models, the dependent variable has three possible outcomes corresponding to the three groups described above with the first group (concordant) serving as the reference category. In essence, two logistic-type regression models are constructed for each of the two discordant groups relative to the reference group of concordance. The same variables are included in each logistic regression model but the coefficients, β, are allowed to vary. Interpretation of each odds ratio is as the odds ratio of being in a particular group (e.g., underestimation) compared to the reference (concordance) for a specific predictor.

Correlates of discordance examined included sociodemographic factors such as age, education and gender as well as behavioral (e.g., alcohol use, clinic satisfaction) and clinical characteristics of patients (e.g., duration of ART, number of prior regimens). Variables were retained in final multivariate models based on statistical significance ($p < 0.05$) and *a priori* designation of key confounders (age, gender, median household income, cost of ART per month, WHO clinical stage, treatment duration of current regimen).

A subset analysis was conducted among 200 persons who were randomly selected for virologic testing. While these 200 participants did not differ socioemographically from the 70 participants for whom viral load was not determined (data not shown), participants who had a viral load performed were less likely to be adherent than those who did not (69% versus 85%; $p = 0.007$). We assessed the association between type of adherence assessment and virologic suppression using logistic regression. Data analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC) and STATA version 9.0 (Stata Corporation, College Station, TX).

Results

Among 279 participants enrolled, two provider surveys were missing adherence information leaving 277 for analysis. Most study participants were male (202; 72.9%), with a median age of 39 years. The level of education was: none, 12 (4.3%); some primary school, 24 (6.6%); some middle, secondary school, 189 (67.7%); and some postsecondary education 52 (18.8%). The median reported individual annual income ($n = 191$) was Indian rupees (international normalized ratio [INR]) 60,000 ($1,333 USD).

Of 277 participants, 223 (80.5%) were on three or more antiretroviral medications. Two hundred sixty-seven (96.4%) participants were on a twice-a-day dosing schedule. The median number of pills per day was 3 (interquartile range [IQR] 2–4). Two hundred thirty-eight (86.0%) participants purchased ART at the clinic where treatment was received, typically for a period of 30 days (85.9%).

By provider assessment, 40.1% of participants were considered adherent (e.g., taking ≥95% of doses), substantially lower than 73.6% adherence determined by participant self-report (Table 1). Discordance between participant self-report

Table 1. Agreement Between Patient Self-Reported Adherence and Physician Assessment of Adherence

		Physician assessment of adherence (% agreement)		
Self reported adherence[a]	n[b]	*≥95%*	*70%–94%*	*<70%*
≥95%	204	80 (39.2)	69 (33.8)	55 (27.0)
70%–94%	44	24 (54.6)	14 (31.8)	6 (13.6)
<70%	29	7 (24.1)	11 (37.9)	11 (37.9)
Total	277	111	94	72

[a]Self-reported adherence assessed by calculating percent of doses missed over a 4-day period.
[b]$n = 277$.
Weighted $\kappa = 0.058$ (95% CI 0.011–0.126).
CI, confidence interval.

and physician estimate was 62.1%. Of the participants considered adherent by their physician 27.9% had <95% adherence by participant self-report (overestimation). Conversely, 60.8% of participants that physicians considered nonadherent had ≥95% adherence (underestimation).

In the subset of 200 participants whose viral load was obtained, viral suppression was associated with participant self-reported adherence (odds ratio [OR] 3.08; 95% confidence interval [CI] 1–65-5.74; $p < 0.05$), but not with provider estimated adherence (OR 1.2; 95% CI 0.67–2.14; $p = 0.54$) (Table 2).

Using participant self-reported adherence as the referent, sensitivity, specificity, negative and positive predictive values of physician estimated adherence were 39.2%, 57.5%, 61.3%, and 42.5%, respectively. The weighted κ coefficient describing agreement between provider estimate of adherence and participant self-report was low, $\kappa = 0.058$ (95% CI 0.011–0.126).

Characteristics and proportions of patients according to whether the adherence estimate by the physician relative to patient self-report was concordant, an overestimate or an underestimate are shown in Table 3. In univariate analysis, a number of characteristics were significantly associated with physician underestimation of adherence. Physicians were more likely to underestimate adherence for participants who were employed. Physician underestimation was also associated with having less than median household income. In addition, higher cost of ART was associated with increased odds of underestimation as was having a history of at least one prior ART regimen (compared to initial regimen). Physicians were also more likely to underestimate adherence for persons with a CD4 cell count 200–350 compared to those who had a CD4 < 200; however, no difference was observed for the groups with CD4 > 350. Both age and longer duration of current ART regimen were negatively associated with physician underestimate of adherence. The only factor associated with overestimation of adherence was age >50 years.

In multivariate analysis, the correlate that remained independently and positively associated with physician underestimation of participant adherence was higher cost of ART per month and independently and negatively associated was increasing age (Table 4). The correlate that remained independently and negatively associated with physician overestimating participant adherence was age greater than 50. Median household income while not significantly associated, suggested association in both underestimating and overestimating physician adherence.

Discussion

While many factors beyond adherence influence treatment response, adherence is a critical factor in improving HIV treatment outcomes. In resource-limited settings where patients are often unable to afford virologic testing to monitor and interpret treatment response, there is a greater reliance on adherence assessment. Other behavioral methods have been considered. Bisson et al.[16] have found pharmacy claim adherence data predicted virologic failure better than CD4 monitoring. Martin et al.[17] compared a medication event monitoring system (MEMS), pill counts, and self-reported adherence among U.S. youth and their caregivers. MEMS provided the most reliable measure of adherence, but the authors suggested pill counts might be used where cost of MEMS is prohibitive. In a systematic review, Wise and Operario[18] concluded that there is insufficient evidence to support use of electronic reminder devices in order to improve adherence. However, there is no gold standard for assessing adherence. We used self-report as the referent to measure adherence as has been done in several other studies of adherence[19] and found a poor correlation between physician estimate of adherence and patient self-report in our Indian private sector setting. Physician estimate of adherence was no better than chance. This finding is consistent with other studies that have demonstrated the inaccuracy of provider estimates of their patients' adherence to therapy in developed countries such as the United States.[5,8,9,20] In our Indian private sector setting an individualized approach to ART care is predominantly practiced, similar to that of the United States.

Table 2. Association Between Physician Estimate and Patient Self-Report of Adherence with Virologic Suppression

	HIV-1 RNA level, copies/mL			
	≥400	*<400*	*OR (95% CI)*	p *Value*
Physician estimated adherence $n = 198$[a]				
Nonadherent (%)	35 (34.3)	67 (65.7)	1	
Adherent (%)	37 (38.5)	59 (61.5)	1.2 (0.67–2.14)	0.54
Self-reported adherence $n = 200$				
Nonadherent (%)	34 (54.8)	28 (45.2)	1	
Adherent (%)	39 (28.3)	99 (71.7)	3.08 (1.65–5.74)	0.05

[a]One hundred ninety-eight physician estimates were completed on the 200 participants who received an HIV viral load measurement.
OR, odds ratio; CI, confidence interval.

Table 3. Characteristics of Patients According to Whether the Adherence Estimate by the Physician Relative to Patient Self-Report was Concordant, an Overestimate or an Underestimate

Characteristics	*No. of observations*	*Concordance* n *(%)*	*Underestimate* n *(%)*	*OR (95% CI)*	*Overestimate* n *(%)*	*OR (95% CI)*
Age, years old						
<30	22	3 (13.6)	15 (68.2)	Referent	4 (18.2)	Referent
30–39	123	48 (39.0)	60 (48.8)	**0.25 (0.07–0.91)**	15 (12.2)	0.23 (0.05–1.17)
40–49	93	35 (37.6)	38 (40.9)	**0.22 (0.06–0.81)**	20 (21.5)	0.43 (0.09–2.11)
≥50	39	19 (48.7)	17 (43.6)	**0.18 (0.04–0.73)**	3 (7.7)	**0.12 (0.02–0.82)**
Gender						
Male	202	71 (35.2)	101 (50.0)	Referent	30 (14.9)	Referent
Female	75	34 (45.3)	29 (38.7)	0.60 (0.34–1.07)	12 (16.0)	0.84 (0.38–1.83)
Marital status						
Married	203	78 (38.4)	97 (47.8)	Referent	28 (13.8)	Referent
Single	29	8 (27.6)	15 (51.7)	1.51 (0.61–3.74)	6 (20.7)	2.09 (0.67–6.55)
Widowed/divorced	45	19 (42.2)	18 (40.0)	0.76 (0.37–1.55)	8 (17.8)	1.17 (0.46–2.98)
Level of education[a]						
None, primary or secondary	225	82 (36.4)	106 (47.1)	Referent	37 (16.4)	Referent
Some college or postgraduate	52	23 (44.2)	24 (46.2)	0.81 (0.43–1.53)	5 (9.6)	0.48 (0.17–1.37)
Employment						
No	78	38 (48.7)	31 (39.7)	Referent	9 (11.5)	Referent
Yes	199	67 (33.7)	99 (49.8)	**1.81 (1.03–3.19)**	33 (16.6)	2.08 (0.90–4.81)
Alcohol						
Never	111	47 (42.3)	48 (43.2)	Referent	16 (14.4)	Referent
Ever	166	58 (34.9)	82 (49.4)	1.38 (0.82–2.34)	26 (15.7)	1.32 (0.63–2.74)
Individual income, median per year, INR (US$)[b]						
≥60,000 (1,333)	111	36 (32.4)	56 (50.5)	Referent	19 (17.1)	Referent
<60,000 (1,333)	80	31 (38.8)	37 (46.3)	1.30 (0.69–2.44)	12 (15.0)	1.37 (0.57–3.23)
Household income median per year (US$)[c]						
≥79,000 (1756)	105	32 (30.5)	57 (54.3)	Referent	16 (15.2)	Referent
<79,000 (1756)	105	53 (50.5)	36 (34.3)	**2.63 (1.43–4.76)**	16 (15.2)	1.67 (0.73–3.70)
Cost of ART per month INR (US$)[d]						
<1200 (<27)	66	37 (56.1)	10 (15.2)	Referent	19 (28.8)	Referent
1200–19999 (27–44)	59	21 (35.6)	30 (50.9)	**5.29 (2.16–12.92)**	8 (13.6)	1.39 (0.43–4.47)
2000–2999 (44–67)	55	16 (29.1)	33 (60.0)	**7.63 (3.04–19.13)**	6 (10.9)	2.39 (0.85–6.71)
≥3000 (≥67)	93	29 (31.2)	57 (61.3)	**7.27 (3.17–16.67)**	7 (7.5)	1.23 (0.36–4.22)
Duration of current ART, months[e]						
<6	76	25 (32.9)	43 (56.6)	Referent	8 (10.5)	Referent
≥6–11	70	22 (31.4)	36 (51.4)	0.95 (0.46–1.96)	12 (17.4)	1.70 (0.59–4.93)
≥12	127	56 (44.1)	49 (38.6)	**0.51 (0.27–0.95)**	22 (17.3)	1.23 (0.48–3.13)
Number of prior regimens						
First-line	151	66 (43.7)	54 (35.8)	Referent	31 (20.5)	Referent
Second-line	65	22 (33.9)	38 (58.5)	**2.11 (1.12–3.99)**	5 (7.7)	0.48 (0.17–1.40)
Third or more-line	61	17 (27.9)	38 (62.3)	**2.73 (1.39–5.37)**	6 (9.8)	0.75 (0.27–2.09)
CD4 T cell count, cells/mm^3[f]						
<200	50	26 (52.0)	17 (34.0)	Referent	7 (14.0)	Referent
200–349	79	26 (32.9)	40 (50.6)	**2.35 (1.07–5.16)**	13 (16.5)	1.86 (0.64–5.40)
350–499	67	23 (34.3)	33 (49.3)	2.19 (0.98–4.94)	11 (16.4)	1.78 (0.59–5.34)
≥500	75	28 (37.3)	37 (49.3)	2.02 (0.92–4.43)	10 (13.3)	1.33 (0.44–4.00)

Concordance, physician and patient self-report were in agreement; underestimate, physician assessing <95% adherence while patient self-report was ≥95%; overestimate, physician assessing ≥95% adherence while patient self-report was <95% adherence.

[a]The level of education none n = 12 (4.3%); some primary school n = 24 (6.6%); some middle, secondary school n = 189 (67.7%).

[b]$n = 191$, [c]$n = 210$, [d]n = 277, [e]n = 273, [f]n = 271.

OR, odds ratio; CI, confidence interval.

In our study, physicians both overestimated and underestimated their patients' adherence, with underestimates prevailing; 44.8% of physician responses were underestimates while 11.2% were overestimates. Physician estimate of adherence was only slightly more specific than sensitive; physicians were better at classifying nonadherent patients as non-adherent than adherent patients as adherent. Underestimating adherence may limit investigation into other clinical factors potentially responsible for treatment failure such as improper dosing or combinations, drug–drug interactions, primary drug resistance, because nonadherence is misidentified as the cause of treatment failure. Overestimation may lead to unnecessary regimen changes or viral resistance, yet failure may merely be related to nonadherence and a missed opportunity to intervene.[5] Previous studies found physicians both underestimating and overestimating adherence, and while some studies found physicians were more likely to overestimate adherence,[9–11,21] our study and others

Table 4. Independent Correlates of Underestimation and Overestimation of Provider Estimated Adherence Relative to Patient Self-Report

Characteristics	*Underestimate (95% CI)*	*Overestimate (95% CI)*
Age, years		
<30	Referent	Referent
30–39	**0.16 (0.04–0.69)**	0.32 (0.05–1.98)
40–49	**0.12 (0.03–0.56)**	0.56 (0.09–3.63)
>50	**0.15 (0.03–0.71)**	**0.10 (0.01–0.86)**
Gender		
Male	Referent	Referent
Female	0.53 (0.26–1.11)	0.67 (0.27–1.65)
Household income, median, INR (US$)		
<79,000 (1,756)	Referent	Referent
≥79,000 (1,756)	1.92 (0.95–3.85)	2.56 (0.99–6.67)
Cost of ART per month, INR (US$)		
<1200 (<27)	Referent	Referent
1200–1999 (27–44)	**3.90 (1.44–10.57)**	0.60 (0.21–1.76)
2000–2999 (44–67)	**6.32 (2.25–17.73)**	0.66 (0.20–2.21)
≥3000 (≥67)	**4.79 (1.77–12.96)**	0.41 (0.12–1.33)
WHO clinical stage		
Clinical stage I and II	Referent	Referent
Clinical stage III	1.36 (0.48–3.85)	0.87 (0.31–2.43)
Clinical stage IV	2.69 (0.94–7.73)	0.53 (0.16–1.72)
Treatment duration, current regimen (months)		
<6 months	Referent	Referent
6–12 months	1.40 (0.61–3.22)	1.75 (0.54–5.71)
>12	0.89 (0.42–1.88)	1.24 (0.42–3.62)

Referent is concordance between physician estimate and patient self-report.
CI, confidence interval; INR, international normalized ratio; ART, antiretroviral therapy; WHO, World Health Organization.

found physicians were more likely to underestimate their patients adherence.[5,22]

Few studies have identified correlates associated with discordance between physician and patient self-report of adherence. In multivariate analysis Murri et al.[21] found unemployment and low education as correlates of discordance. However, we did not find either to be associated in underestimating or overestimating patient adherence. This difference in findings may be due to our participant group in general representing a demographic of relatively well-educated, middle-income, HIV-infected persons seeking care in private clinics located in one of India's highest HIV-prevalent cities. We found persons in whom adherence by the physician was underestimated were more likely to be paying more for their ART and less likely to be under 30 years of age. Higher ART payments reflect more costly second- and third-line regimens. Physicians may have underestimated their patients' adherence, given their failure on a first-line regimen. We found no independent correlates associated in physician overestimating patient adherence. However, while not statistically significant, there was a trend with median household income being associated with both overestimating and underestimating physician adherence, perhaps suggesting the arbitrary nature of physician estimates of their patients' adherence.

Unlike patient self-report, which we showed correlated with virologic suppression, physician estimation of adherence did not correlate with virologic suppression. This finding is consistent with other studies that, despite overestimates of adherence by self-report, found adherence to be significantly associated with plasma HIV concentrations.[5,7,11–13]

There are several limitations to our study. First, it is cross-sectional in design and therefore does not reflect the dynamic nature of adherence. Participants were attending private clinics and volunteered to complete a survey about their HIV care and treatment including ART adherence. In addition, our participant group is predominantly urban, relatively well-educated and middle income. Therefore, our results do not necessarily reflect practices in other settings and may limit the generalizability of our findings. Future studies might include participants seeking care in rural or public clinics, where a public health approach to ART is largely practiced and where persons are generally of lower educational and economic status or in settings serving a mix of demographic groups. Second, the participants' and the physicians' questions and their response options for adherence differed, perhaps leading to some measurement error. For participants we used the patient adherence questionnaire that has been validated for self-report.[15] However, since this questionnaire is not applicable to providers, we used a direct way of asking the physicians to estimate their patients' adherence. Third, this study used a self-reported questionnaire, which the patient's physician was not privy to, perhaps promoting more candid participant responses and may not be equivalent to the more likely clinical practice of direct questioning by the physician. Fourth, we had limited ability to detect independent correlates associated with physician overestimates of patient adherence given the small number of persons in this group.

Improving the ability of providers to assess adherence is essential for routine care of HIV-infected persons, especially in settings where second- and third-line therapy is limited, and viral load and resistance testing to guide treatment is limited if

not absent. The success of ART in India will in part depend on patient ART adherence and their physicians' ability to assess their adherence and intervene as necessary. Research to date suggests physicians are unable to reliably assess their patients' adherence to therapy and we identified this to be the case in our Indian setting. While underlying causes of discordance may require further investigation, our results suggest potential biases are present when physicians assess adherence and therefore argue for a less subjective tool.

Two reviews have demonstrated the validity of self-reported adherence. In the review by Simoni et al.,[23] self-reported adherence was significantly correlated with HIV viral load in 57 of 67 (85%) recall periods assessed. In addition, in the meta-analysis by Nieuwkerk and Oorts[24] of 65 studies, they found the pooled OR of detectable plasma viral load in persons who self-reported nonadherence was 2.31 (95% CI 1.99–2.68). While most of the reviewed studies have been conducted in the West,[23] we found a similar association in our population. Because the data collectively suggest that patient self-report obtained using brief, validated questionnaires performs significantly better than physician assessment of adherence, it may be a more valid alternative. However, continued research into low-cost, validated adherence measures that can be assessed rapidly and with precision is critical in order to improve adherence assessment. This is particularly needed in resource-limited settings, where expensive monitoring and access to second- and third-line ARVs are not readily available.

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Author Disclosure Statement

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Address correspondence to:
Louise Walshe, B.S.N., M.P.H.
Johns Hopkins Bloomberg School of Public Health
615 North Wolfe Street, E6531
Baltimore, MD 21205

E-mail: lwalshe@jhsph.edu