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Developing Useful HAART Adherence Measures for India: The Prerana Study

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To the Editors

Excellent adherence to antiretroviral regimens is closely associated with achieving HIV viral suppression and preventing the development of drug resistant virus. Missed doses, interruptions in therapy, and improper dosing can all lead to HIV drug resistance [e.g. 1–3]. Like many other areas of behavior change, long term maintenance of consistent adherence has been a challenge for behavior change in the U.S., and data from Africa [4] indicate that adherence levels may decline over time in developing country settings as well. Reliable and valid adherence measures are essential to the study of HAART adherence and to evaluate the impact of adherence interventions, [e.g. 5–9]. To be useful in clinical settings, they also need to be brief and relatively simple to administer [10]. Although multiple adherence measures have been found to predict viral load, there is no single gold standard for the assessment of adherence [8] and most measures have been developed in the US [e.g. 11,12]. In India, Shah et al. [13] found a cross-sectional association between past 4 day adherence and viral load in a subsample of their study in Pune and Delhi. However, no Indian studies to date have examined, in a prospective fashion, the impact of adherence on viral load, the predictive validity of combined measures, or the relationship between multiple adherence measures. This study was designed to address this gap by assessing the relationship between multiple self-reported adherence measures and HIV viral suppression in a longitudinal cohort of HIV infected patients in Bangalore, India.

The study was conducted in the outpatient department of medicine in a catholic hospital in Bangalore, India. Eligibility criteria included being at least 18 years old; capable of communicating in English, Kannada, Tamil, or Telugu; being HIV infected, on anti-retroviral medication for at least one month, and willing to participate in all follow-up visits. Following referral by their physicians or our NGO collaborators, participants were brought to a private room for informed consent and an approximately 1-hour study interview. Blood was drawn at the baseline, 6-month and 12-month visits, by trained, hospital-based phlebotomists. 229

participants were enrolled in the study. The present analyses include data on those who participated in both the baseline and 12-month follow up visits (n=203).

The instruments were developed in English and translated into Kannada, Telugu, and Tamil. All translations were independently back-translated into English to ensure equivalence.

Adherence was assessed using five different self-report measures: 1) A modified version of the first question in the AACTG self-reported adherence instrument [14], using a detailed dose-by-dose assessment of adherence in the past 4 days; 2) A calculation of the percent missed doses in the past week; 3) A calculation of the percent missed doses in the past month; and 4) A Visual Analogue Scale [10] in which participants were shown a line, with numbers ranging from 0–100 and asked to point to the place that best indicated the proportion of pills taken in the past month.

We also assessed treatment interruptions, defined as number of occasions on which the patients had missed all their medication for two or more consecutive days.

HIV plasma viral load tests were performed by Reliance Life Sciences laboratories using Real Time PCR assay with fluorescein labeled Taqman probe for quantitation of HIV particles. The test was developed and its performance characteristics determined at Molecular Diagnostics and Genetics, Reliance Life Sciences. The specificity of the assay is >98% and its sensitivity enables detection of 100 viral particles per ml. [15]

The adherence measures were treated as continuous variables to calculate Pearson correlation coefficients. All adherence rates were also dichotomized at ≥ 95 % to examine their relationship with viral load. Chi-square analyses were performed to assess the relationship between detectable viral load and the dichotomized adherence rate and treatment interruption variables. All statistical analyses were done using SPSS 15.0 [16].

At baseline, the majority of the sample reported being married (76%), male (69%), Hindu (88%) and employed (73%). Virtually all were living with their extended (52%) or "nuclear" (42%) families, either in Bangalore (41%) or elsewhere in the state of Karnataka (43%). The mean age was 38 (range: 23–74). Participants reported having been diagnosed with HIV for a mean of 3 years and 5 months (range: 1–206 months) and taking antiretroviral medication for a mean of 21 months (range: 1–133 months). Virtually all (98%) of the participants were on an NNRTI-based regimen, with the most common regimens being lamivudine/stavudine/nevirapine (49%), followed by lamivudine/zidovudine/nevirapine (26%), lamivudine/zidovudine/efavirenz (8%), and lamivudine/stavudine/efavirenz (7%).

From 83% to 92% of participants reported ≥95% adherence during the different assessment periods. All self-reported adherence measures were significantly correlated at $p < .001$, with correlation coefficients ranging from .8 to .93. At the end of the study, half of the sample reported having experienced at least one treatment interruption, of at least 48 hours in length. Twenty-eight percent of the participants had a detectable viral at that time.

As shown in Table 1, all adherence measures were significantly associated with viral suppression. We next examined whether data on treatment interruption history would improve our ability to predict viral suppression above and beyond these standard adherence measures. Only optimally (≥95%) adherent participants (n=169) were included in this analysis. The results showed that among optimally adherent participants, having a history of one or more treatment interruptions was significantly associated with a lower likelihood of viral suppression than among participants who did not report any treatment interruptions (68% and 85%, respectively, <.01). The inclusion of treatment interruption data correctly classified an

additional 61% (23/38) of optimally adherent participants who presented with detectable viral load.

By 12 months, 11 participants (5%) had died and another 15 participants (6%) were lost to follow-up. There were no significant baseline differences between cohort members and dropouts with regard to any of the demographic variables, or adherence. However, drop-outs did have a significantly lower mean baseline CD4 count than those who remained in the study (174 vs. 321 cells per mm^3, $t = 4.65$, $P < 0.001$).

These data show high rates of self reported adherence during the past month, comparable to rates reported by study participants in the US, Europe and Africa, using similar measures [e.g. 9]. Treatment interruptions appear to be the most common form of non-adherence in this setting. Since this behavior is typically not reported in the adherence literature, we do not know if this is comparable to behaviors in other resource-constrained settings. The self-reported adherence measures used in this study were significantly associated both with each other and with viral load, suggesting that they are indeed valid measures of pill taking. Research settings may require multiple measures and should include viral load, whenever possible. However, given that the more complex and time consuming measures did not perform any better than the simpler ones, a brief measure such as the VAS may be more feasible in clinical settings.

It should be noted that these results were obtained in an urban, private, non-profit, private setting in South India and may not generalize to other geographical regions or to public clinic settings, where the accuracy of self-report may be impacted by different factors. It should also be noted that the self-reported adherence assessments were conducted in a confidential setting, which may have increased the accuracy of self-report. Finally, the instrument was administered by highly trained study staff who were not associated with the hospital's clinic staff. Participants often report wanting to please their medical providers when asked about adherence.

The data show high rates of virologic failure in this sample, in spite of high rates of self-reported adherence. This is similar to results reported by Shah [13], who called for the large-scale introduction of second line therapy by the Indian government. We echo this request and note that these rates may indicate the beginning of an epidemic of drug resistant HIV in India. More research is needed to examine this issue and to develop programs that will improve adherence, minimize treatment interruptions and maximize the efficacy of first line regimens, which remain the primary form of treatment in both private and public clinic settings in India.

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Table 1

Percent of participants with undetectable viral load (at 12 months).

Adherence	VAS-month % (n)	1-mo % missed % (n)	1-week % missed % (n)	ACTG 4-day % (n)
≥ 95 %	78 % (131)	76 % (141)	77 % (131)	75 % (136)
< 95 %	47 % (16)	35 % (6)	50 % (16)	52 % (11)
	$\chi^2(1) = 13.14$, P = 0.001	*$\chi^2(1) = 12.80$, P = 0.001*	*$\chi^2(1) = 9.55$, P < 0.01*	*$\chi^2(1) = 4.71$, P < 0.05*

VAS=Visual Analogue Scale of adherence

ACTG 4-day= adherence in the last four days