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Comparison of Subjective and Objective Adherence Measures for Pre-Exposure Prophylaxis against HIV Infection among Serodiscordant Couples in East Africa

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ABSTRACT

Background: Pre-exposure prophylaxis (PrEP) efficacy is highly dependent on adherence. Yet, it is unclear which adherence measures perform best for PrEP.

Methods: We compared three types of self-reported (SR) adherence questions (rating of ability to adhere, frequency of doses taken, percent of doses taken) and three forms of objective adherence measurement (unannounced pill counts [UPC], electronic monitoring [EM], plasma

tenofovir levels) using data from an ancillary adherence study within a clinical trial of PrEP among East African serodiscordant couples (Partners PrEP Study). Monthly measures were assessed for the first six months of follow-up.

Results: 1,147 participants contributed 6,048 person-months of data to this analysis. Median adherence was high: SR rating (90%), SR frequency (93%), and SR percent (97%); UPC (99%); and EM (97%). Prevalence of steady state daily dosing (SSDD; ≥40 ng/mL) was 74% in a random subset of tenofovir samples obtained from 365 participants. Discrimination of SSDD versus less than SSDD levels was poor for SR rating (area under the receiver operating curve [AROC] 0.54), SR frequency (AROC 0.52), SR percent (AROC 0.56) and UPC (AROC 0.58), but moderate for EM (AROC 0.70). Correlation was moderate among self-reported measures, adherence (0.61-0.66), but low for these self-reported measures compared with UPC (0.32-0.36) and with EM (0.22-0.28).

Conclusions: EM was the only adherence measure with meaningful ability to discriminate between SSDD and less than SSDD plasma tenofovir levels. Correlation between subjective and objective measures was poor. Future research should explore novel approaches to adherence measurement as PrEP moves into demonstration projects and programmatic implementation.

Keywords: adherence; objective adherence; subjective adherence; PrEP; Serodiscordant; TFV; drug levels

INTRODUCTION

Oral tenofovir-based pre-exposure prophylaxis (PrEP) can reduce HIV transmission by over 90%[1,2]; however, the efficacy of PrEP is highly dependent on adherence[3]. An accurate understanding of adherence behavior is therefore critical for interpretation of clinical trial data, as well as anticipating the individual and public health benefits of PrEP as it begins to be used in demonstration projects and clinical settings[4].

Measurement of adherence is challenging. Currently available methods include self-reported adherence, clinic-based pill counts, unannounced pill counts (UPC), pharmacy refill frequency, drug concentrations, and electronic monitoring (EM). Each adherence measurement method has its limitations and no gold standard exists[5]. Although UPC, EM, and drug levels are objective methods; they are still susceptible to manipulation[6-9]. For example, individuals can remove pills from bottles just prior to clinic visits without taking them to appear more adherent than they really are, or they may take a pill just prior to a clinic visit only because they are aware that their blood will be drawn for a drug level measurement. UPC may be less susceptible to manipulation, [10,11], but the logistics of conducting unannounced visits can be challenging and costly. Self-reported adherence measures are an inexpensive alternative that have been shown to correlate with objective measures for antiretroviral therapy (ART) adherence[12]. Self-report, however, can be subject to recall bias and are often overestimated owing to social desirability[12,13]. Importantly, two clinical trials of PrEP (FEM-PrEP and VOICE) found very high self-reported adherence, yet drug detection was very low[14-16]. Similarly, a recent detailed analysis of PrEP adherence in the iPrEx trial showed large discrepancies between self-report and drug detection[17].

Additional data are needed on optimal adherence measurement strategies for PrEP. Self-report would be ideal for use in clinical settings, given its low-cost and ease of implementation; however, few studies to date have presented detailed comparisons of self-reported measures to objective measures for PrEP adherence[17-19]. Importantly, questions used for self-reported adherence vary and some questions may be more accurate than others in a given population because of individual and/or cultural preferences. Moreover, the cognitive processes involved in recalling adherence behavior beyond a few doses are likely more of an estimation (e.g., rating of ability to take medication as prescribed) than an enumeration (e.g., frequency or percent of doses taken)[20]. Previous studies have found self-reported rating of adherence to more closely align with objective measures than frequency or percent[21-23]; however, no such studies had been performed for PrEP in a resource-limited settings.

In this analysis, we compared three types of self-reported adherence questions (rating of ability to adhere, frequency of doses taken, and percent of doses taken) with three forms of objective adherence measurement (UPC, EM, and plasma tenofovir levels) using data from an ancillary adherence study within a clinical trial of PrEP among serodiscordant couples in East Africa (the Partners PrEP Study).

METHODS

Partners PrEP Study

The Partners PrEP Study was a phase III, randomized, double blind, placebo-controlled, three arm clinical trial conducted on the HIV uninfected partner of 4,747 serodiscordant couples at nine research sites in Kenya and Uganda. Enrolment began in July 2008 and concluded in

November 2010. The HIV-uninfected partner was randomly assigned to one of three arms: once daily tenofovir (TDF), combination emtricitabine/tenofovir (FTC/TDF), or identical placebo. Study design, procedures and outcomes have been previously described[24]. In July 2011, the independent Data and Safety Monitoring Board recommended discontinuation of the placebo arm after the TDF and FTC/TDF arms had demonstrated 67% and 75% efficacy, respectively.

Partners PrEP Ancillary Adherence Study

In November 2009, an ancillary study was initiated to objectively measure and support adherence at three of the Uganda Partners PrEP Study sites (Kabwohe, Kampala, and Tororo). A convenience sample of 1,147 individuals was selected from participants enrolling in the main study or those already enrolled who had at least six months left of follow-up. Study participants were selected from all three study arms. Details of the ancillary adherence study have also been previously described[1].

Adherence measurements

In the Partners PrEP Study, adherence was measured by pill counts at monthly study visits and blood was stored for later selected determination of plasma tenofovir levels. Tenofovir levels were quantified by the Clinical Pharmacology Analytical Laboratory at the Johns Hopkins University School of Medicine using previously described ultra-performance liquid chromatographic-tandem mass spectrometric methodologies[25]. Calibration standards for assay ranged from 0.31 to 1,280 ng/mL[25]. The lower limit of detection was 0.31ng/mL. In the ancillary adherence study, adherence was additionally measured by three methods:

1) Pill counts at unannounced home visits, which were performed approximately monthly for the first six months, then quarterly thereafter (i.e., participants were told such visits would be conducted but the day was not specified);
2) Electronic pill bottles (the medication event monitoring system, or MEMS) from which data on bottle openings was downloaded at monthly study visits; and
3) Self-reported questions administered at monthly study visits. Following a short preamble to normalize adherence challenges, the following three types of self-report assessments were administered:
    A) Self-reported (SR) rating- "Please tell me your ability to take study pill." (responses categorized as very poor, poor, fair, good, very good, excellent);
    B) Self-reported (SR) frequency- "Did you take your study tablets all the time?" (responses categorized as none of the time, a little of the time, some of the time, a good bit of the time, most of the time, all of the time); and
    C) Self-reported (SR) percent- "What percent of the time were you able to take the study tablets exactly as directed?" (categorized in 10% increments, ranging from 0 to 100%).

Ethics Statement

The human subjects committees of Massachusetts General Hospital/Partners Healthcare, the University of Washington, the Centers for Disease Control and Prevention, the Uganda National Council for Science and Technology, and the Uganda Virus Research Institute Science and Ethics approved the study protocol.

Statistical Analysis

We analyzed the first six months of PrEP use in the ancillary adherence study for each participant. This time period was chosen because all adherence measurements were collected monthly and could be readily compared. As has been done previously[21], SR rating and SR frequency response categories were assigned quantitative adherence in 20% increments. For example, the lowest category (e.g., "very poor" for SR rating) was assigned 0% and the highest category (e.g., "all of the time" for SR frequency) was assigned 100%. UPC adherence was calculated as the number of pills expected for the month minus the pills present at the count divided by the number of days in the month. EM adherence was compiled as the total number of pill bottle openings divided by the number of days of interest (e.g., 28 days in the month). Staff openings of the EM bottles and days when a protocol-defined drug hold was in effect (e.g., for adverse events or pregnancy) were excluded. Adherence was capped at 100% (e.g., when the openings exceeded the number of days in the month). EM was also similarly calculated for the seven days prior to the collection of samples for tenofovir determination to match the window for detection of tenofovir in plasma[26]. Steady state daily dosing (SSDD) was defined as drug levels $\geq$40 ng/mL[25]. In a sensitivity analysis, we further explored the threshold consistent with any dosing in the past week (>0.31 ng/mL)[25].

We investigated the predictive validity, correlation, and bias among the adherence measures. Predictive validity was assessed in three ways. First, we constructed a GEE model for each self-reported measure regressed against SSDD plasma tenofovir. Second, we plotted receiver-operating curves for each measure against SSDD plasma tenofovir and compared the area under the curve. Lastly, we used linear models to assess the proportion of variation in tenofovir levels

explained by each of the subjective and objective measures (indicated by R^2); measures were assessed individually and then in combination. To test correlation, we computed the Spearman rank correlation coefficient (rho) on monthly adherence. We computed the bias for each self-reported measure as the difference between the measure and the monthly EM adherence, and tested the hypothesis of no bias using generalized estimating equations (GEE) with Huber White sandwich standard errors. The level of statistical significance was set at 5%. All statistical analyses were conducted using Stata 13.0.

RESULTS

Participant characteristics

A total of 1,147 participants contributed 6,048 person-months with a median follow-up of 5.5 in the ancillary adherence study (interquartile range [IQR] 5.5, 5.5) months per participant. Participants were followed for a minimum and maximum of 1 and 6 months, respectively, in this analysis. Participant characteristics potentially relevant to adherence behavior have been previously described[1]. Briefly, 53% were male and the median age was 34 years (IQR 30, 40). More than half (59%) were farmers with moderate education. The prevalence of heavy alcohol use and depression was 9% and 5% respectively. Duration of prior PrEP use at enrollment into the ancillary adherence study varied from 0 to 19+ months. Nearly all (98%) partners were living together, most (80%) had children together, and a quarter were in polygamous marriages. Approximately two thirds of the couples (66%) had disclosed their HIV serodiscordant status to another person.

Adherence

The median adherence was 90, 93, and 97% for the self-reported measures (SR rating, SR frequency, and SR percent, respectively), and 99%, and 97% for UPC and EM respectively; the data were generally left-skewed (Figure 3). The median time between EM openings was 24 hours (IQR 23.5-24.5); the median number of >48 hour gaps between EM openings over the six-month analysis period was 2 (IQR: 1-6). Perfect (100%) adherence was most common with SR frequency and UPC (66% of participant-months in each method) and least common with SR rating (50% of participant-months). Less than optimal adherence (<80%)[1] was most commonly seen with SR rating (10% of participant-months) and EM (12% of participant-months). Of note, 18% of participant-months for EM were capped because of adherence >100%. Eighty-nine percent of these exceeded the anticipated adherence by ≤2 additional doses (i.e., 100-110% adherence). Tenofovir drug levels were assessed on 486 randomly selected blood samples taken from 365 participants (32%) in the ancillary adherence study. Age, gender and study arm distribution in these 365 participants were similar to the that of the total cohort in the adherence study[1]. Prevalence of SSDD was 74% (n=358) of the 486 samples.

Predictive validity

As shown in Figure 1, mean adherence was non-significantly higher in participants with SSDD plasma tenofovir levels compared to those with less than SSDD: 89% versus 85% (p=0.08) for SR rating, 93% versus 91% (p=0.18) for SR frequency, and 96% versus 93% (p=0.05) for SR percent. In examining the objective measures, mean adherence was significantly higher in participants with SSDD versus those with less than SSDD: 97% versus 92% (p=0.02) for UPC, 93% versus 72% (p<0.001) EM adherence for the 28 days prior to sample collection for tenofovir determination, and 94% versus 79% (p<0.001) for 7 days prior to sample collection. Of

all adherence measures, EM explained the most variability (5.5%) in tenofovir levels. Inclusion of any or all other adherence measures explained an additional <1%.

As shown in Figure 2, the area under the receiver-operating curve (AROC) for all self-reported measures and for UPC was low (0.51-0.54). EM adherence showed the highest AROC of 0.70 (95% CI, 0.64, 0.76) for the 7 days and 0.68 (95% CI, 0.61, 0.74) for the 28 days prior to collection of the tenofovir samples. In the sensitivity analysis considering the threshold consistent with any dosing in the past week (>0.31 ng/mL), we found no differences in the magnitude of discrimination for any adherence measure compared with the SSDD threshold. Discrimination of SSDD with UPC , however, lost statistical significance (p=0.09).
Of note, of the 128 participant-months with less than SSDD, 43 participant-months from 40 participants were found to have 100% EM adherence for the seven days prior to sample collection.

Correlation

As shown in Table 1, pairwise spearman's correlation (rho) of monthly self-reported adherence ranged between 0.32 and 0.36 when compared with UPC and between 0.22 and 0.28 when compared with EM. Correlation among the self-reported measures ranged between 0.61 and 0.66. All correlations were statistically significant (p<0.001).

Bias

Overall mean EM adherence was 3.9 percentage points (95% confidence interval 3.1, 4.8; p<0.001) higher than SR rating. However, it was 0.7 percentage points (CI -1.5, 0.2), p=0.12)

lower than SR frequency and 3.3 percentage points (CI -4.1, -2.5), p<0.001) lower than SR percent. As shown in Figure 4, pairwise agreement was generally better at higher levels of adherence (≥80%) compared to lower levels of adherence. At these lower levels, mean EM adherence was higher than SR frequency, as well as for SR rating.

DISCUSSION

In a cohort of East African serodiscordant couples participating in a clinical trial of PrEP, adherence was high by multiple forms of self-report, unannounced pill counts and electronic monitoring; tenofovir drug levels were moderately high. Despite the similarities in overall adherence values (e.g., medians), correlation between subjective and objective measures was poor and only electronic monitoring was able to meaningfully discriminate between steady state and less than steady state daily dosing plasma tenofovir levels. Tenofovir drug levels serve as an important benchmark for comparison with other adherence measures, because they document medication ingestion. Like any adherence measure, however, drug levels have limitations, including assay failure, variable drug metabolism within and among individuals, and a relatively short half-life in plasma[26]. Additionally, a dose taken just prior to determination of a drug level will mask non-adherence in the prior several days. Our findings underscore the complexity in accurately measuring adherence behavior.

The three self-reported measures had similar inability to discriminate between SSDD and less than SSDD tenofovir with AROCs equivalent to a coin flip. The recent analysis within the iPrEx trial also found low predictive validity for self-reported adherence with an AROC of approximately 0.5[17]. Similarly, in the FEM-PrEP trial, the positive predictive value of self-

reported adherence compared to tenofovir levels was low, ranging between 28.7% and 42.2% when averaged over time[16].

The poor correlation between subjective and objective measures (rho: 0.22-0.36) was likely due in part to social desirability and recall bias in self-reported adherence measurements, and is consistent with prior studies of both PrEP and ART adherence[12,17,19,27]. The statistical significance of these correlations is likely driven by the large number of participant-months, rather than clinically meaningful relationships. Of note, the low level of correlation may be partially explained by the clustering of self-reported adherence values in this analysis (i.e., six categories for SR rating and SR frequency and 11 categories for SR percent) compared to continuous adherence with the objective measures. Importantly, within the TDF2 trial, a correlation analysis yielded a phi coefficient of 0.28[18] and moderate correlation has been seen with self-report and drug levels for ART[28]. It is therefore possible that self-report may have limited validity in some settings.

Correlations among the three types of self-reported measures (rho: 0.61-0.67) were higher; however, the distribution of the three self-reported measures differed. SR rating had the widest distribution and identified individuals with low adherence, suggesting that this type of adherence question may be most informative for identifying adherence challenges. Similar findings have been seen in prior analyses of ART adherence measurements[21-23]. Indeed, the goal with self-reported adherence is often described as "pulling people off the ceiling"-- even if self-reported adherence is overestimated, those reporting less than perfect adherence may benefit from additional adherence support.

Interestingly, average SR rating was lower than EM adherence. Self-reported adherence is typically higher than objective measures, suggesting that individuals may have underestimated their adherence when creating this type of adherence estimation. Lower self-reported adherence when the corresponding EM adherence was also low or moderate has been observed previously[29,30], suggesting that participants may be overly self-critical whenever their adherence is less than optimal. Cognitive testing has been used to understand the performance of different types of self-report[31] and may be beneficial in this setting to understand how this population views adherence behavior. Alternatively, higher EM than self-reported adherence may have been introduced by extra EM openings unassociated with dosing.

This analysis also identified noteworthy findings among the objective adherence measures. First, a low rho correlation was found between UPC and EM adherence (0.4). While predictive validity for UPC was statistically significant, discrimination between SSDD and less than SSDD plasma tenofovir was lower than that of EM (AROC 0.58 versus 0.68, respectively). These findings suggest UPC may have been subject to manipulation (e.g., pill dumping despite the unannounced nature of the pill count). One potential limitation of the comparisons of UPC and EM with plasma tenofovir is the difference in monitored times in which UPC and EM reflect one month of adherence behavior, whereas the window for detection of tenofovir in plasma is seven days. The findings for 28-day and 7-day EM adherence, however, are similar. Overall, 43 participant months had 100% 7-day EM adherence, but less than SSDD tenofovir suggesting that in some cases, participants may have manipulated the EM devices (e.g., opening the device without taking the pill), although assay failure and/or atypical drug metabolism could have impacted the

tenofovir findings. Importantly, the number of participants with highly discrepant adherence by EM and plasma tenofovir level reflects only 11% of participants randomly selected for tenofovir level determination).

The strength of this analysis lies in the large sample with multiple measures of adherence; however, there are also limitations. First, the time frames associated with the subjective and objective adherence measures were mismatched compared to the tenofovir drug quantification (28 versus 7 days) as noted above, and only EM adherence could be adjusted. Additionally, a sample of participants was used for determining plasma tenofovir levels among approximately one-fifth of the cohort. Although the sampling was random, some bias may have been present.

In sum, adherence is paramount for PrEP efficacy in reducing HIV transmission, yet characterizing adherence behavior remains challenging. While the low cost and ease of implementation associated with self-reported adherence makes it an ideal candidate for adherence measurement in future studies and clinical implementation of PrEP, our findings suggest that self-reported adherence may be inaccurate, even when geared toward estimation rather than enumeration. Moreover, objective adherence measures have limitations in accuracy as well, including possible manipulation and/or technical failures. Future efforts should explore novel approaches to PrEP adherence measurement. For example, cognitive testing may help identify more informative self-report questions[31]. SMS may allow for more frequent assessment of self-report, thus reducing recall bias, as well as potentially reducing social desirability through the relative anonymity of the technology. Real-time adherence monitoring may improve accuracy of EM through rapid identification of technical failures, and also has the added

potential for delivery of real-time adherence feedback and/or intervention[32,33]. Pharmacokinetic measures (e.g., drug levels in dried blood spots, hair)[19,34,35] that provide an understanding of adherence over longer time periods compared with plasma are desirable[36]. These or other measurement approaches will be critical for defining the adherence-efficacy relationship as PrEP is rolled out beyond clinical trials. Ongoing assessment of adherence behavior in demonstration projects and programmatic implementation will be important, because motivations, facilitators, and barriers to adherence may differ (e.g., known PrEP efficacy, intensity of counseling).

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Figure 1: Comparisons of self-reported (SR) adherence, unannounced pill counts (UPC) and electronic monitoring (EM) with detection of steady state daily dosing (SSDD) of plasma tenofovir levels.

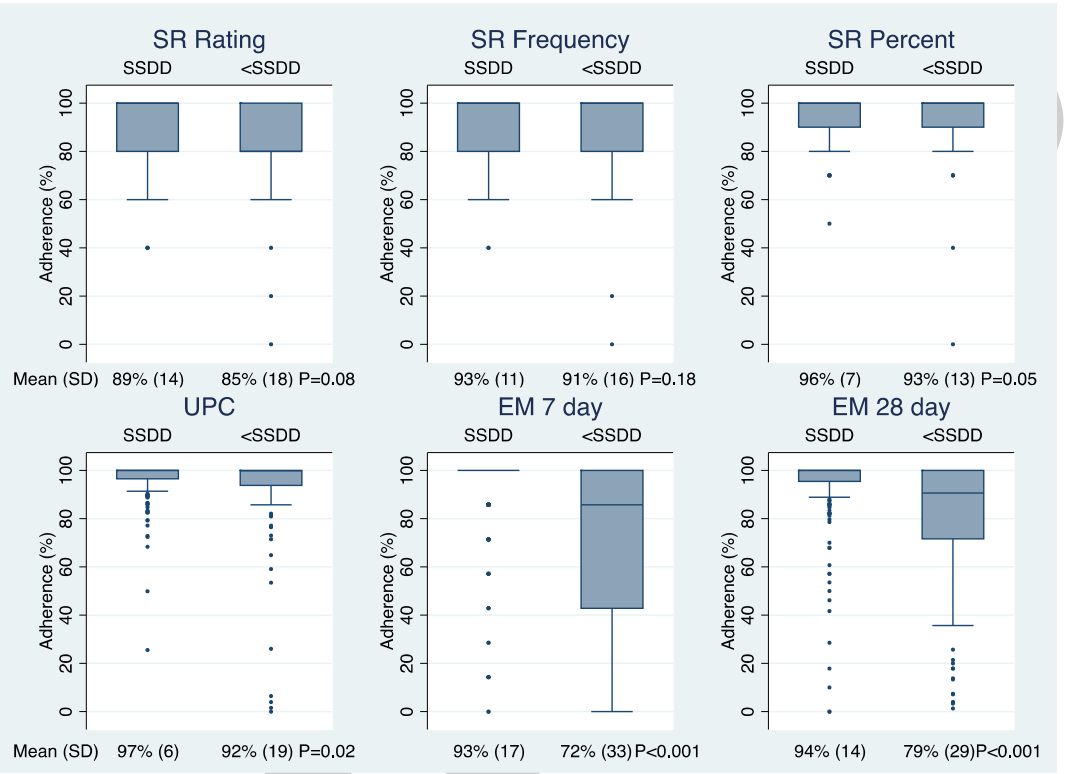


Figure 2: Receiver operating curves for the sensitivity of self-reported (SR) adherence, unannounced pill counts (UPC), and electronic monitoring (EM) to detection of steady state daily dosing plasma tenofovir levels.

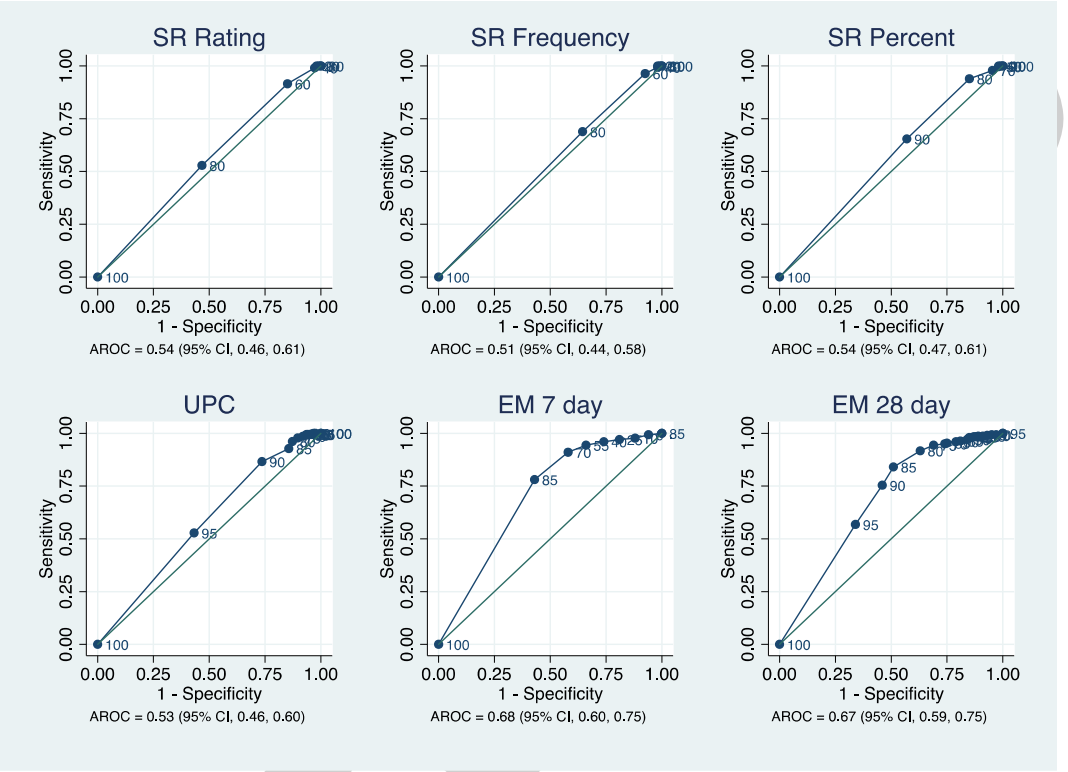


Figure 3: Distribution of monthly adherence by self reported (SR) adherence, unannounced pill counts (UPC) and electronic monitoring (EM)

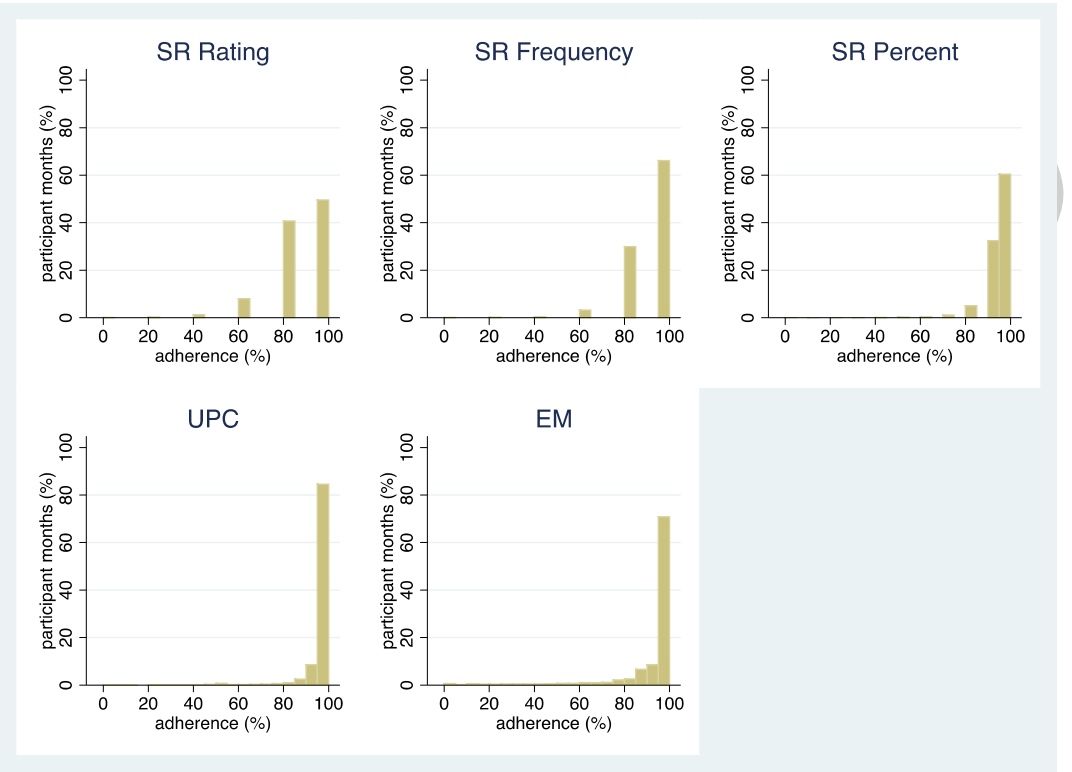
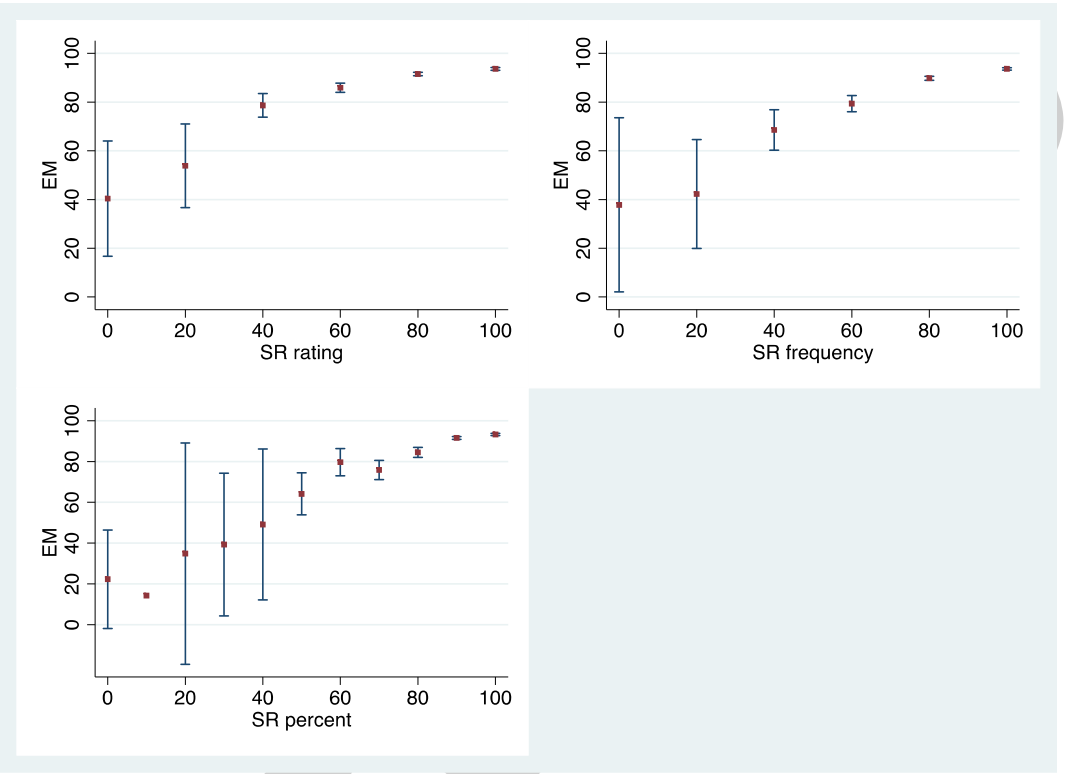


Figure 4: Distribution of self-reported (SR) adherence and corresponding mean electronically monitored (EM) adherence. The dots show the mean MEMS adherence for each self-report category and the bars reflect the 95% confidence interval of the EM adherence.



Note: There was a single observation at 10% SR percent and therefore no 95% confidence interval

*Table 1: Spearman's correlation coefficients among self reported (SR) measures, unannounced pill counts (UPC) and electronic monitoring (EM)**

	SR rating	SR frequency	SR percent	UPC	EM
SR rating	1				
SR frequency	0.66	1			
SR percent	0.61	0.63	1		
UPC	0.32	0.36	0.35	1	
EM	0.22	0.28	0.24	0.40	1

*All findings were statistically significant (P<0.001).