## Title
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# Study product adherence measurement in the iPrEx placebo-controlled trial: Concordance with drug detection

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## Abstract

**Objective—**To evaluate the concordance between adherence estimated by self-report (in-person interview or computer-assisted self-interview [CASI]), in-clinic pill counts, and pharmacy dispensation records and drug detection among participants in a placebo-controlled, pre-exposure prophylaxis (PrEP) HIV prevention trial (iPrEx).

**Design—**Cross-sectional evaluation of 510 participants who had drug concentration data and matched adherence assessments from their week-24 study visit.

**Methods—**Self-reported adherence collected via (1) interview and (2) CASI surveys, (3) adherence estimated by pill count, and (4) medication possession ratio (MPR) were contrasted to having a detectable level of drug concentrations (either tenofovir diphosphate [TFV-DP] or emtricitabine triphosphate [FTC-TP]) as well as to having evidence of consistent dosing (TFV-DP≥16 fmol/$10^6$ cells), focusing on positive predictive values (PPV), overall and by research site.

**Results—**Overall, self-report and pharmacy records suggested high rates of product use (over 90% adherence); however, large discrepancies between these measures and drug detection were noted, which varied considerably between sites (PPV from 34% to 62%). Measures of adherence performed generally well in the US sites, but had poor accuracy in other research locations. MPR outperformed other measures but still had relatively low discrimination.

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**Conclusions—**The sizable discrepancy between adherence measures and drug detection in certain regions highlights the potential contribution of factors that may have incentivized efforts to appear adherent. Understanding the processes driving adherence reporting in some settings, but not others, is essential for finding effective ways to increase accuracy in measurement of product use and may generalize to promotion efforts for open-label PrEP.

**Keywords**

PrEP adherence; self-report; drug concentration; drug detection; iPrEx

## INTRODUCTION

Measuring actual rates of study product use in randomized placebo-controlled HIV pre-exposure prophylaxis (PrEP) trials continues to challenge research communities. [1] The most commonly used strategy for quantifying adherence to prescribed regimens in standard practice is self-report. [2] Specific to adherence to HIV antiretroviral regimens, self-report has been consistently associated with viral load, although associations are small to moderate and self-report appears to consistently overestimate adherence when compared to electronic drug monitoring by 5 to 15%. [3] In contrast, self-report of product use in PrEP randomized controlled trials (RCTs) grossly overestimated product use in several trials. For example, despite very high adherence, as measured by self-report and product return, in both the FEM-PrEP [4] and VOICE [5] trials, actual drug exposure was measured in a quarter or less of participants who were tested. Similarly, participants in the iPrEx trial [6] reported high rates of product use, while actual drug exposure was detected in about half of those participants tested, although this varied substantially by research site [7]. To date, there has been limited research exploring the discrepancies between objective measurements of drug exposure and self-reported adherence to study product, as well as other commonly used methods to characterize adherence in RCTs.

We examined data collected during the iPrEx RCT. The iPrEx study was a randomized, double-blind, placebo-controlled trial of daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) versus placebo among 2,499 men and transgender women who have sex with men (MSM/TG) from sites in Peru, Brazil, Ecuador, the United States, Thailand, or South Africa. Primary and follow-up analyses of the iPrEx study showed protective effects of FTC/TDF PrEP against HIV acquisition when offered with a comprehensive package of prevention services. [6]

The current study aimed to both characterize study product adherence in the iPrEx RCT by the method used to collect these data (self-report from (1) in-person interview documented on a Case Report Form [CRF] and (2) via a computer-assisted self- interview [CASI], (3) in-clinic pill counts and (4) refill-based medication possession ratio [MPR]) and to evaluate the accuracy or concordance between these measures and objective drug detection within a subsample of participants in the active arm (FTC/TDF) who had drug concentration data available at week-24.

# METHODS

## Participants

The iPrEx study population was men and transgender women who have sex with men (demography and all study procedures, included regulatory and ethics approvals, for the main trial have been previously described [6]). For this substudy, all available week-24 drug levels (drug levels obtained between week-18 and week-30 study visits) were used. Individuals with drug levels were those on study product at time of the drug level test and who were involved in one or more of three separate iPrEx sub-projects; (1) the DEXA substudy evaluating bone density, (2) controls for the case-control substudy evaluating efficacy in relation to drug levels, and/or (3) samples taken from sites in Ecuador, Peru and the US to evaluate drug levels among those self-reporting varying levels of adherence. In this latter group, among participants at the 4 Andean sites, self-report on interview was used to categorize groups into 100%, 90–99%, and less than 90% adherent, or “don’t know”/no answer provided. Up to 10 participants were randomly selected from each of these groups; where there were fewer than 10, all available samples were evaluated. For the US sites, a random sample regardless of reported rates of adherence was selected. The subsample analyzed combines all available drug level tests from the substudies noted above. Because our aim was to evaluate the accuracy of various measures of adherence against an objective criterion of drug detection, and the subprojects noted above had collected week-24 drug levels, we selected week-24 data as having the most data coverage.

## Procedures

Participants in the iPrEx study were dispensed a bottle of 30 FTC/TDF (or placebo) tablets at enrollment and each monthly visit and were advised to take one tablet each day. Participants were asked to bring back their study product bottles, whether used or not used, at all visits. At visits when participants brought back partially used bottles, site pharmacists counted the remaining tablets, re-dispensed them to the participant if appropriate (e.g. the bottle had an intact label and tablets were in good condition), and advised the participant to finish taking the tablets from the opened bottle before the unopened bottle. All bottles and number of tablets dispensed and returned were documented on study case report forms (CRFs) by study staff. Self-reported adherence was collected in person by research personnel at all monthly visits. Self-reported data via CASI was collected at quarterly visits and at the visit when participants stopped taking the study product. We evaluated all of these measures for the purpose of this analysis among active arm participants with drug concentration tests available at the 24-week visit.

## Drug Concentration Testing

Tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) concentrations were quantified in viably cryopreserved peripheral blood mononuclear cells (PBMC) using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay as previously described. [6, 8] PBMC concentrations reflect dosing over an approximate 1 to 2-week period depending on the regularity of dosing preceding the drug holiday. Additionally, some between-participant variability is expected due to differences in metabolism of TDF/FTC. PBMC concentrations are less susceptible to recent (“white coat”) dosing than plasma

concentrations, which reflect dosing in the previous 2–3 days. The lower limit of quantitation for TFV-DP and FTC-TP in PBMCs was 2.5 fmol and 0.1 pmol per sample, respectively. Drug detection was defined as a concentration in the quantifiable range of the assay. The proportion of participants with any drug detection (either TFV-DP or FTC-TP) was determined and evaluated in relation to adherence measures. We also evaluated each adherence measure using a TFV-DP concentration cut-off of ≥16 fmol/$10^6$ cells, which has been associated with a 90% reduction in HIV acquisition in prior regression analyses and estimated to reflect consistent dosing (more than 2 doses per week on average [8]).

## Adherence Measures

Measures of adherence were collected every month except the CASI-based assessment, which was quarterly. Four measures of adherence relative to the participant's week-24 study visit were analyzed for this report. (1) In-person interview adherence was the self-reported number of days on which the participant missed his/her dose *since last drug dispensation* (for iPrEx this would typically reflect the past 4-weeks and was variable by site in terms of who collected the data) on CRFs. (2) CASI items asked about the percentage of days in the *past 3 months* that doses *were* taken, which could range from 0 to 100% in 10% increments. (3) Calculated percent adherence by pill count was based on amount of product dispensed at the prior visit (typically, the week-20 study visit), minus the number of tablets returned at the week-24 visit, divided by the days between these two visits, and multiplied by 100. This value could range from 0% to over 100%. If bottles were not returned, tablets from the unreturned bottle were assumed to have been used. (4) MPR represented the ratio of days "covered" by a dispensation relative to the total number of days between visits. Specifically, this was calculated as the number of days covered by tablets dispensed at the prior visit divided by the number of days between the prior and week-24 visit. This method relied only on dispensation of drug at the visit prior and days elapsed between visits and does not adjust for returned product at week-24. A value of 1.25 was used to reflect high "adherence" (essentially meaning that the participant would have had 25% more days covered than actually needed). This value was in part based on study protocol (visits scheduled every 28 days with a visit window of +/− 5 days), dispensation practices (re-dispensation of unused product when appropriate), and the participants' attendance to their scheduled visits. Thus, MPR values above 1.00 indicate 100% coverage or higher, with 1.25 indicative of the highest rates of coverage, and values below 1.00 reflect days uncovered by study drug.

## Adherence Strata

Self-report and pill count measures were classified into the following categories: ≥100% adherence, 90–99% adherence, 50–89% adherence, <50% adherence, or don't know/ missing. Because perfect (≥100%) adherence over a one-month period or more was anticipated to be uncommon and this group may differ substantively between those with any missed dose(s), perfect adherence to study product was identified as a separate strata, followed by high but not perfect adherence (90–99%). The adherence levels below 90% used a broad range in response to a sparse distribution of individuals reporting lower ranges of adherence. MPR was classified as ≥1.25, 1.00 – <1.25, 0.50 – <1.00 and <0.50.

### Statistical Analyses

Descriptive analyses were used to characterize adherence estimates using the four adherence measures in terms of percentage of participants classified by each measure as perfect (100% or higher), high (90–99%), mid-range (50–89%) and low (<50%) levels of adherence, as well as among those reporting "don't know" or having missing data.

To evaluate the accuracy of these reports in relation to drug detection, the proportion with drug detected among those active-arm participants with available drug detection data was characterized per adherence level, focusing on positive predictive value (PPV; proportion of those who are expected to have drug detected given their reported adherence and who did have drug detected) for the higher adherence levels and on negative predictive value (NPV; proportion without drug detected among those reporting adherence <50%). We also examined overlap between drug detection and regular product use by contrasting proportions with drug detected and proportion with TFV-DP concentrations ≥16 fmol/$10^6$ cells.

Adherence measures were evaluated for association with each other using Spearman's rank-order correlation. Adherence measures were also evaluated using area under the curve (AUC), estimated using the c-statistic in logistic regression, to assess the ability of each measure to correctly discriminate between those with and without drug detection. As a general guide to interpretation, an AUC of 0.50–0.60 indicates no discrimination, 0.60–0.70 indicates poor discrimination, 0.70–0.80 indicates fair discrimination, 0.80–0.90 indicates good discrimination, and 0.90–1.0 indicates excellent discrimination. Because previous work identified that drug detection varied significantly by site [7], all analyses are presented by site and across sites. Statistical analyses were conducted in SAS 9.3.

## RESULTS

### Participant demography

The study sample included 510 participants. The demography of this sample, in comparison to those in the active arm of iPrEx not included in the sample, is presented in Table 1. Among the 510 participants in the study sample, 51% were 25 years of age or younger, 14% were transgendered, and 28% reported college education. At baseline, 315 (62%) reported condomless receptive anal intercourse in the past three months, 250 (49%) reported drinking ≥5 drinks when drinking in the past month. Across most demographic variables the sample included did not significantly differ from those excluded (those in the active arm that did not have drug level testing results available). Unique to the sample, participants from Brazil were under-represented and participants from the US and the Africa/Asia sites were slightly over-represented. Those included in the sample analyzed also appeared to perceive risk for HIV-infection to by somewhat more likely (12% of those included in the sample and 23% of those not included reported HIV-infection was unlikely; $p < .01$). Participants included in the sample were also more likely to have reported an STI (within the prior 6-months) at baseline, 31% of included versus 24% of excluded participants. Perceptions of arm assignment, efficacy of PrEP, report of condomless sex at baseline, number of partners and other demographic variables did not differ. On average, those included and those excluded in the analyzed sample were similar in report of adherence on interview (94% and 95%,

respectively), CASI (89% and 90%, respectively), pill count (99% and 98%, respectively) and MPR (1.39 and 1.38, respectively), with no significant differences between groups.

### Rates of adherence by method

Across this sample of 510 participants in the active arm who had drug concentrations available, about half reported adherence below 100% (Table 2). Pill count and MPR had lower proportions of individuals falling below the "perfect" strata. As indicated in Table 3, any drug detection was identified in 53% of individuals in this subsample, with 31% having TFV-DP≥16 fmol/$10^6$ cells. These estimates varied considerably by region.

### Concordance, PPV and NPV

Concordance between estimated high levels of adherence and drug detection are presented in Table 4. Among those reporting perfect adherence on in-person interview, 51% had any drug detected, dropping to 35% for having TFV-DP concentrations ≥16 fmol/$10^6$ cells. Similarly, on CASI, 50% of those reporting perfect adherence had any drug detected, and only 29% had TFV-DP concentrations ≥16 fmol/$10^6$ cells. By region, the PPV among perfect and near-perfect self-reporters of adherence was highest in the US and lowest in the Andes. Accuracy between self-report for interview and CASI in terms of PPV with drug detection did not appear to be remarkably different, while NPV of reporting <50% adherence on interview with *not* having drug detected did appear stronger than reports collected from CASI. Reporting perfect adherence on interview had a lower PPV than reporting high, but not perfect, adherence in all but the US sites (Table 4).

For measures based on product return and dispensation records, concordance with drug detection was variable. MPR appeared generally more concordant with drug detection; however, for both pill counts and MPR, accuracy appeared low in relation to ≥16 fmol/$10^6$ cells concentration levels.

### Correlations between measures

Correlation between measures, and between each measure and drug detection, is presented in Table 5. Self-report on interview was modestly correlated with all of the other adherence measures. Pill count and MPR were also modestly correlated with each other, but neither was correlated with self-report on CASI. In AUC analysis, the only adherence measure that was able to discriminate between participants with and without drug detection was MPR, with relatively poor discriminatory ability (AUC 0.64, 0.59–0.69).

## DISCUSSION

We identified discrepancies between self-reported (interview and CASI), pill count and MPR-based adherence estimates and drug detection that varied by study site/location, with the US sites having greater consistency between measured adherence and drug detection. A report of perfect adherence had lower concordance with drug detection than reporting some missed doses. Procedurally, at most sites at the time of week-24 study visits, a report of no missed doses was generally associated with briefer discussions about product use, less probing for reasons doses were missed, and positive reinforcement for achieving perfect

adherence; a report of any missed dose(s) often led to longer discussions, probing, and messaging stressing accountability and need to improve. This may have inadvertently incentivized perfect adherence reports, as those would largely eliminate requests to engage in discussions about adherence or ways to improve it.

In the opposite direction of self-report on interview, those with highest MPR had higher PPV than those in the “high but not perfect” range (90–99% adherence). Further, MPR outperformed all other measures in AUC analysis. As mentioned, MPR relies only on pharmacy dispensation records, and is not affected by self-report or return of product, so this indicator may be less influenced by social desirability bias. MPR relies heavily on study retention and less on procedures that are often incomplete despite retention (e.g., retuning of unused product or study product bottles). Retention allowing for dispensation can be thought of as a necessary but insufficient condition for high rates of adherence. Failure to return for study visits within appropriate windows, alternatively, may be a valuable marker for potential non-adherence that appeared generally more reliable than self-report or pill counts, per se.

Adherence in diverse therapies generally tends to be around 60% [9], with perfect adherence being uncommon (cf., [10]) and self-report (in contrast to electronic measurement of dose taking) overestimates adherence by an average of 12.7%[11] to 14.9%[12, 13]. The iPrEx RCT did not use electronic monitoring. Quantitative drug concentrations provided the opportunity to evaluate concordance between the adherence measures and having TFV-DP concentrations ≥16 fmol/$10^6$ cells. The discrepancies identified between perfect adherence and drug detection for all but the US study sites are high, suggesting intentional non-adherence and over-reporting and are also comparable to discrepancies recently reported among women participants in the MTN-001 cross-over study [14].

The high concordance between self-report and pill count based adherence and the discordance between each of these measures and drug detection bears further exploration. For self-report, recall based measures have known error variance attributable to a myriad of factors well described in the literature (e.g., demands on and distortions to recall given complexity/simplicity or regularity of the target behavior, length of recall period, and cognitive processes [3, 15]). Whereas some degree of memory and cognitive error is expected, the size of the discrepancy observed between self-report and drug detection in many sites exceeded what would be expected from “forgetting about forgotten doses.” The size and variability across sites in these differences suggests social desirability or self-presentation bias which may be driven by social factors, beliefs about the research and participation in it, or community factors (see for example [16]). Self-report and announced product count will likely be particularly inaccurate where the social contract between the participant and the research project is characterized by high perceived benefits of participation, low perceived benefits of actually using the study product (potentially high perceived costs of using the product), and high concern over being removed from the trial if non-adherent. In this regard, announced pill counts are susceptible to many of the biases typically associated with self-report. Strategies to mitigate factors that incentivize over-reporting were implemented within iPrEx towards the latter half of the study [17] and included removal of reinforcement of reports of perfect adherence (no missed doses),

reassurance that adherence problems would not lead to discontinued or depreciated participation in the trial, and use of neutral assessment approaches. The effect of these changes has not been formally evaluated, although are clearly consistent with current recommendations for quality standards in use of self-report [3].

Limitations in the current study included having drug concentrations only for a subset of participants at their week-24 on-study visit, which is not representative of adherence over time. Analyses of drug detection in a random sample of week-8 serum/plasma found somewhat lower drug detection in the US region, with overall detection across all sites estimated at 55% [18]. Further, the concordance strategy used to examine self-report, pill counts and MPR, and drug detection is limited in terms of mismatched time frames for each method and that which would be captured by drug concentrations in PBMC, which captures dosing behavior over approximately the prior one to two weeks. As previously noted, this necessitated focus on those who would have been expected to have drug detected, leaving the strata for adherence below perfect difficult to disentangle and poorly characterized. Targeted research with matched time frames is needed. Organization of results by study region was implemented on the basis of available data. However, sites that were grouped over large geographies (e.g., Africa and Asia combined) or even proximal ones (e.g., Lima, Peru and Guayaquil, Ecuador within the Andes-region) to increase sample sizes per region are clearly unique in multiple social-cultural and structural-resource factors. Our results highlight differences between regions but cannot speak to the causes or nature of these differences. Finally, these results are specific to the subsample included in these analyses and the manner in which we operationalized adherence from the available measures. Adherence rates are necessarily reflective of our specific criteria for defining different strata for adherence. Further, the drug detection rates are also specific to this sample. While concordance between adherence measures and drug detection would be expected to be similar for participants not included in this analysis, overall rates of drug detection in this sample may not be representative of the overall iPrEx cohort. Such estimates require an inclusive or truly random sampling strategy.

Adherence measurement and monitoring specific to clinical trials evaluating self-administered biomedical interventions has received increasing attention [1]. Our results suggest that accuracy in measuring adherence is driven in part by region specific factors which likely includes varying degrees of intentional non-adherence and over-reporting. These factors are less apparent is in the US cohorts; consistently, the US sites in iPrEx RCT demonstrated higher rates of product use [7] and accuracy in reporting. While self-report may provide valuable insights and information for participants similar to those in the US iPrEx research sites, it poorly characterized adherence in other research regions. Additional targeted research on adherence measurement specific to RCTs of biomedical HIV prevention strategies to identify factors influencing intentional non-adherence or over-reporting of product use is critically needed. Qualitative work exploring reasons for and context surrounding both study medication adherence and comfort around reporting of non-use among iPrEx participants [19, 20] highlight the opportunity for gathering insights on participant experiences. Additionally, targeted research unpacking factors unique to adherence in HIV-prevention research studies in diverse communities is emerging [16, 21] and should be included in behavioral science agendas.

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**TABLE 1**

Baseline demography of iPrEx active arm, participants included in subsample analyzed and those excluded from analyses

| Variable | | All Active Arm iPrEx Participants (N=1251) | Included in subsample (Drug level tested at week-24; N=510) | Excluded from subsample (Drug level not tested at week-24; N=741) | p-value for difference between included and excluded[a] |
|---|---|---|---|---|---|
| Site | | | | | < 0.001[b] |
| | Brazil | 186 (15%) | 33 (7%) | 153 (21%) | |
| | Andes | 850 (68%) | 348 (68%) | 502 (68%) | |
| | USA | 113 (9%) | 56 (11%) | 57 (8%) | |
| | Africa/Asia | 102 (8%) | 73 (14%) | 29 (4%) | |
| Age | | | | | 0.35 |
| | ≤ 20 | 270 (22%) | 100 (20%) | 170 (23%) | |
| | >20–25 | 387 (31%) | 160 (31%) | 227 (31%) | |
| | >25–30 | 236 (19%) | 94 (18%) | 142 (19%) | |
| | > 30 | 358 (29%) | 156 (31%) | 202 (27%) | |
| Education | | | | | 0.28 |
| | Less than HS | 279 (23%) | 101 (20%) | 178 (25%) | |
| | High School | 675 (55%) | 266 (53%) | 409 (56%) | |
| | College | 280 (23%) | 139 (28%) | 141 (19%) | |
| Transgender | | 163 (13%) | 70 (14%) | 93 (13%) | 0.55 |
| Number of sexual partners (prior 3-months) | | | | | 0.53 |
| | ≤1 | 113 (9%) | 46 (9%) | 67 (9%) | |
| | >1–5 | 423 (34%) | 151 (30%) | 272 (37%) | |
| | >5–10 | 264 (21%) | 116 (23%) | 148 (20%) | |
| | >10 | 451 (36%) | 197 (39%) | 254 (34%) | |
| Reported condomless anal receptive intercourse (prior 3-months) | | 732 (58%) | 315 (62%) | 417 (56%) | 0.11 |
| Frequency of drinking alcohol (prior month) | | | | | 0.81 |
| | <2–3 per week | 377 (31%) | 147 (29%) | 230 (31%) | |
| | ≥ 2–3 per week | 861 (70%) | 359 (71%) | 502 (69%) | |
| 5 or more drinks per drinking occasion (prior month) | | 666 (53%) | 250 (49%) | 416 (56%) | 0.252 |

| Variable | | All Active Arm iPrEx Participants (N=1251) | Included in subsample (Drug level tested at week-24; N=510) | Excluded from subsample (Drug level not tested at week-24; N=741) | p-value for difference between included and excluded[a] |
|---|---|---|---|---|---|
| Perceived PrEP Efficacy | | | | | 0.89 |
| | >0 and <50% | 116 (11%) | 55 (11%) | 61 (10%) | |
| | 50–99% | 305 (28%) | 127 (26%) | 178 (29%) | |
| | 100% | 125 (11%) | 52 (11%) | 73 (12%) | |
| | Don't Know | 553 (50%) | 247 (51%) | 306 (50%) | |
| Perceived Likelihood of HIV infection | | | | | 0.01 |
| | Not Likely | 213 (19%) | 57 (12%) | 156 (23%) | |
| | Could Happen | 736 (64%) | 322 (69%) | 414 (61%) | |
| | Probably/Almost Certain | 193 (17%) | 88 (19%) | 105 (16%) | |
| Reported STI in past 6-months | | 336 (27%) | 156 (31%) | 180 (24%) | < 0.001 |
| Depressed | | 60 (5%) | 32 (6%) | 28 (4%) | 0.19 |
| Co-habitation with partner | | 97 (8%) | 38 (8%) | 59 (8%) | 0.85 |
| Concern over employment status | | | | | 0.92 |
| | Not Concerned | 388 (32%) | 154 (31%) | 234 (32%) | 0.924 |
| | Somewhat/very Concerned | 834 (68%) | 341 (69%) | 493 (68%) | |
| Perceived arm assignment at 12-week study visit | | | | | 0.427 |
| | Placebo | 108 (10%) | 45 (9%) | 63 (10%) | |
| | Don't Known | 738 (66%) | 329 (67%) | 409 (65%) | |
| | Active (TDF/FTC) | 278 (25%) | 119 (24%) | 159 (25%) | |

[a] Controlling for site;

[b] Site not controlled for in this specific test only.

**TABLE 2**

Distribution of adherence overall and by region among active arm participants with drug detection data available at week 24 (N=510)[a]

| SELF-REPORT MEASURES | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Self-report on interview | | | | | Self-report on CASI | | | | |
| | Andes | Africa/Asia | Brazil | U.S. | Total | Andes | Africa/Asia | Brazil | U.S. | Total |
| Median (IQR) | 100% (95–100%) | 97% (92–100%) | 100% (91–100%) | 100% (93–100%) | 100% (94–100%) | 100% (90–100%) | 90% (80–100%) | 95% (90–100%) | 90% (90–100%) | 90% (90–100%) |
| 100% | 57% | 45% | 52% | 55% | 55% | 46% | 24% | 47% | 37% | 43% |
| 90–99% | 19% | 34% | 24% | 27% | 22% | 25% | 31% | 38% | 46% | 29% |
| 50–89% | 13% | 11% | 18% | 14% | 13% | 19% | 20% | 6% | 15% | 18% |
| <50% | 2% | 1% | 3% | 4% | 2% | 1% | 5% | 3% | 0% | 2% |
| Missing or DK | 9% | 8% | 3% | 0% | 7% | 9% | 20% | 6% | 2% | 9% |
| **PHARMACY MEASURES** | | | | | | | | | | |
| | Pill-count | | | | | MPR[b] | | | | |
| | Andes | Africa/Asia | Brazil | U.S. | Total | Andes | Africa/Asia | Brazil | U.S. | Total |
| Median (IQR) | 100% (93–100%) | 100% (91–104%) | 96% (83–100%) | 97% (83%–107%) | 100% (91–103%) | 1.34 (1.11–1.59) | 1.48 (1.15–1.71) | 1.44 (1.21–1.93) | 1.38 (1.13–1.71) | 1.38 (1.12–1.62) |
| ≥ 100% | 61% | 59% | 42% | 48% | 58% | 63% | 70% | 70% | 64% | 65% |
| 90–99% | 17% | 15% | 21% | 21% | 18% | 22% | 19% | 15% | 27% | 22% |
| 50–89% | 16% | 18% | 33% | 16% | 17% | 11% | 8% | 15% | 7% | 10% |
| <50% | 5% | 4% | 3% | 14% | 6% | 4% | 3% | 0% | 2% | 3% |
| Missing or DK | <1% | 4% | 0% | 0% | 1% | 0% | 0% | 0% | 0% | 0% |

DK = Don't know; MPR= Medication Possession Ratio

[a] N by region: Andes=354, Africa/Asia=79, Brazil=35, U.S.=58.

[b] MPR categories: ≥1.25, 1.0–1.25, 0.5–<1.0, and <0.5

## TABLE 3

Percent with any drug detected and percent with drug levels at or above levels associated with consistent dosing high rates of protection (TFV≥16 fmol/$10^6$ cells) [8] N=510

| | Any drug detected | TFV-DP≥16 |
|---|---|---|
| Andes | 44% | 23% |
| Africa/Asia | 63% | 49% |
| Brazil | 58% | 21% |
| U.S. | 95% | 57% |
| **Total** | **53%** | **31%** |

**TABLE 4**

Proportions with drug detected (PPV) among those reporting higher adherence levels and proportion without drug detected (NPV) among those in lowest adherence level (N=510[a])

*Self-Report Measures*

**Any drug detected in PBMCs at 24 weeks**

| | Self-report on interview | | | | | Self-report on CASI | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Andes | Africa/Asia | Brazil | U.S. | Total | Andes | Africa/Asia | Brazil | U.S. | Total |
| PPV: =100% | 48% | 52% | 59% | 94% | 54% | 43% | 62% | 47% | 100% | 50% |
| PPV: 90–99% | 51% | 72% | 75% | 93% | 63% | 48% | 59% | 67% | 96% | 59% |
| PPV: 50–89% | 38% | 75% | 33% | 100% | 49% | 44% | 64% | 100% | 75% | 51% |
| NPV: <50% | 100% | 0% | 100% | 0% | 75% | 50% | 0% | 0% | N/A | 25% |
| NPV: Missing or DK | 81% | 33% | 0% | 11% | 71% | 59% | 45% | 100% | 0% | 56% |

**Drug Concentration ≥16 TFV-DP detected in PBMCs at 24 weeks**

| | Self-report on interview | | | | | Self-report on CASI | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Andes | Africa/Asia | Brazil | U.S. | Total | Andes | Africa/Asia | Brazil | U.S. | Total |
| PPV: =100% | 29% | 45% | 24% | 68% | 35% | 24% | 50% | 13% | 62% | 29% |
| PPV: 90–99% | 29% | 56% | 25% | 40% | 36% | 26% | 47% | 33% | 64% | 36% |
| P-values[b] | 1 | 0.43 | 0.93 | 0.07 | 0.81 | 0.87 | 0.8 | 0.21 | 0.88 | 0.18 |

*Pharmacy Measures*

**Any drug detected in PBMCs at 24 weeks**

| | Pill-count | | | | | MPR[c] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Andes | Africa/Asia | Brazil | U.S. | Total | Andes | Africa/Asia | Brazil | U.S. | Total |
| PPV: ≥ 100%[1] | 44% | 58% | 57% | 89% | 51% | 55% | 73% | 70% | 94% | 63% |
| PPV: 90–99% | 60% | 64% | 57% | 100% | 66% | 35% | 43% | 40% | 93% | 44% |
| PPV: 50–89% | 39% | 77% | 64% | 100% | 53% | 14% | 50% | 20% | 100% | 25% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| NPV: <50% | 95% | 0% | 100% | 0% | 61% | 100% | 0% | 100% | 0% | 94% |
| NPV: Missing or DK | 100% | 67% | 80% | N/A | 75% | | | | | |
| **Proportion with ≥16 TFV-DP detected in PBMCs at 24 weeks** | | | | | | | | | | |
| | Pill-count | | | | | MPR[c] | | | | |
| | Andes | Africa/Asia | Brazil | U.S. | Total | Andes | Africa/Asia | Brazil | U.S. | Total |
| PPV: ≥ 100% or MPR≥ 1.25 | 24% | 40% | 21% | 52% | 29% | 31% | 55% | 22% | 64% | 38% |
| PPV: 90–99% or MPR 1.00 – <1.25 | 40% | 55% | 14% | 50% | 41% | 14% | 43% | 20% | 47% | 23% |
| P-values[b] | 0.02 | 0.37 | 0.7 | 0.91 | 0.03 | 0.005 | 0.43 | 0.93 | 0.91 | 0.001 |

DK= Don't know; MPR= Medication Possession Ratio

[a] N by region: Andes=354, Africa/Asia=79, Brazil=35, U.S.=58.

[b] p values reflect difference in PPV between perfect and high adherers

[c] MPR categories are ordered as: ≥1.25, 1.0–1.25, 0.5–<1.0, and <0.5

[1] Seperation of those returning less product than expected (e.g., >100% adherent) from those characterized as perfectly adherent (100%) did not suggest a difference between these groups.

## Table 5

Association between measures and with any drug detection (N=510[a]).

| | Self-report on interview | Self-report on CASI | Pill-count | Medication possession ratio |
|---|---|---|---|---|
| Self-report on interview | -- | -- | -- | -- |
| Self-report on CASI | r=0.41; p<0.001 | -- | -- | -- |
| Pill-count | r=0.40; p<0.001 | r=0.04; p=0.37 | -- | -- |
| Medication possession ratio | r=0.19; p<0.001 | r=-0.01; p=0.85 | r=0.34; p<0.001 | -- |
| AUC for drug detection by measure (CI) | 0.51 (0.46–0.56) | 0.52 (0.47–0.57) | 0.49 (0.44–0.54) | 0.64 (0.59–0.69) |

[a] AUC = area under the curve; CI = confidence interval. Using Spearman correlation for r coefficients and logistic regression for AUC.