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ORIGINAL PAPER

# The Role of Pharmacy Refill Measures in Assessing Adherence and Predicting HIV Disease Markers in Youth with Perinatally-Acquired HIV (PHIV)

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## Abstract

Antiretroviral (ARV) adherence is critical in monitoring disease response in youth with perinatally-acquired HIV (PHIV). We used pharmacy refill (PR) information for PHIV youth from the PHACS Memory Sub-study to calculate medication availability over 2, 4, and 6 months. PR, a proxy of adherence, was compared with self-reported 7-day adherence in predicting suppressed viral load (SVL < 400 copies/mL) and higher CD4% (≥ 25%). Among 159 PHIV youth, 79% were adherent by 7-day recall, and 62, 55, and 48% by PR over 2, 4, and 6 months, respectively. Agreement between 7-day recall and PR adherence was weak (Kappa = 0.09–0.25). In adjusted logistic regression models, adherence showed associations with SVL for 7-day recall (OR 2.78, 95% CI 1.08, 7.15) and all PR coverage periods (6-month: OR 3.24, 95% CI 1.22, 8.65). Similar associations were observed with higher CD4%. PR measures were predictive of study retention. Findings suggest a possibly independent role of PR adherence measures.

**Keywords** ARV adherence · Pediatric HIV · Pharmacy refill · Self-report · Appointment adherence

## Introduction

Once life-limiting, HIV has been reclassified as a chronic disease to be managed over the lifespan due to improved antiretroviral (ARV) regimens and clinical care, which have transformed morbidity, mortality, and health outcomes. However, linkage to HIV care and maintaining suppressed HIV viral load (SVL) through sustained ARV adherence to optimize long-term health outcomes, reduce risk of drug resistance, and prevent HIV transmission, remains a challenge. In the United States (US), only 19% of those living with HIV have SVL [1]; even more alarming, for youth age 13–29 only 6% maintain SVL [2]. Stringent medication adherence is particularly important for youth with perinatally acquired HIV (PHIV), who as they age up, have higher risk for HIV-related clinical events and mortality [3]. Achieving persistent adherence to ARVs has unique challenges for youth with PHIV as they age into young adulthood, continue to accept their HIV status, transition to anticipated independence and self-care, and prepare to navigate long-term issues associated with managing chronic HIV disease [4–8].

Accurate adherence assessment is essential to monitoring viral response to ARVs and adherence promotion

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interventions. However, existing ARV adherence measures have conceptual, practical and/or cost limitations. Self-reported adherence measures commonly are used to monitor adherence for youth with PHIV, and have been shown to be valid predictors of viral load in these youth. They are brief and easily administered in the clinic setting, at minimal expense. These measures assess adherence over a relatively short period, typically asking about medication-taking in the prior three, seven or 30 days. Despite their practicality, self-reported adherence measures are prone to effects of social desirability, recall bias, and memory. Objective measures of adherence are needed to confirm the role of adherence in health status indicators when validity of self-report is suspect or insufficient. Electronic monitoring devices may be considered the "gold standard" but they are expensive, difficult to implement in routine practice, typically monitor only one medication at a time, and may overestimate true adherence by assuming medication removed from the pill vial was ingested [4, 6, 9–15].

Pharmacy refill (PR) is a promising alternative proxy adherence measure focused on medication availability. Some chronic disease studies, including those among people with HIV, have shown that the performance of PR adherence measures was comparable to electronic adherence monitoring measures [16, 17]. As an adjunct or collateral measure to self-report methods, PR records provide an objective and inexpensive measure that allows for assessment over longer periods of time and may be particularly useful in large epidemiological studies. Unlike self-report measures, PR data are available regardless of whether individuals miss a clinic visit or when circumstances such as cognitive or memory limitations prevent successful administration of self-report questionnaires. PR records are used to construct a proxy measure of ARV adherence defined as the percent of time medication was available over specified observation periods, assuming individuals can only adhere when medication is in their possession (e.g., refilled) [18–22]. Medication availability may indicate an individual's commitment and means to pick up ARV refills on time and may be related closely to the level of true adherence. Poor or inconsistent adherence and failure to pick up ARV refills on time, or in general poor compliance to HIV care including missing a clinic visit, similarly may reflect deficient planning, organizational or other cognitive skills that interfere with optimal adherence [23–30].

Previous studies have suggested that PR adherence is a valid method for monitoring medication adherence in adults with HIV [20, 31–34]. Although available international studies for adolescents with HIV investigated the utility of PR adherence [22, 35–37], studies in the US had smaller sample sizes and were conducted some time ago [17, 38]. Thus, in the era of improved ARV regimens, performance of PR adherence in youth with PHIV in the US and its association with clinical indicators of HIV disease status need to be re-evaluated. Although previous studies examining PR adherence measures have used various lengths of observation [6, 19], the role of observation length has not been extensively studied in youth with PHIV. Additionally, to our knowledge, there have been no systematic studies demonstrating the strength of PR in predicting adherence to clinic visits or study retention. The primary aims of the analyses presented herein were to: (1) explore the characteristics of PR adherence measures and their performance in predicting clinical outcomes for youth with PHIV as compared to self-reported recall adherence measures; (2) evaluate the contribution of medication availability carry-over effects in PR adherence assessments; and as a secondary aim, evaluate the relationships of PR measures with study retention within our study population.

## Methods

### Participants

Evaluated youth with PHIV were enrolled in the Memory Functioning in Children and Adolescents with Perinatal HIV Infection (or Memory) sub-study of the Pediatric HIV/AIDS Cohort Study (PHACS) Adolescent Master Protocol (AMP). The Memory sub-study is a prospective cohort study designed to compare memory and executive functioning in two groups of participants, those with PHIV and those who were perinatally exposed to HIV but uninfected (PHEU), across two visits (baseline and 2-year follow-up). Participants were enrolled between March 2010 and July 2014. Eligibility criteria required participants were 9 to 19 years at entry, and English speaking, from eight participating AMP sites. The analyses presented herein were restricted to PHIV participants who had completed the baseline Memory sub-study visit and were prescribed at least one ARV within the 6 months prior to the baseline visit with available pharmacy data.

The sites involved in this study were all urban, located in medium to large sized cities where the HIV epidemic and research centers tend to be concentrated. Pharmacy access varied across sites, and across participants within sites depending on variables such as insurance provider. Some sites had pharmacies co-located with the HIV clinic; others had arrangements with local pharmacies specializing in HIV care and providing a home delivery service; at others, the site picked up medications on behalf of the patient; or, the patient/family member picked up medications themselves at local community-based pharmacies, such as Walgreens, CVS, etc. In addition, availability of automatic refills varied across sites. For these reasons, separate sensitivity analyses were conducted to account for site effect in models for primary and secondary outcomes.

Both AMP and the Memory sub-study were approved by the Institutional Review Board at each participating site and Harvard T. H. Chan School of Public Health. Informed consent and age-appropriate assent were obtained per institutional guidelines.

## Pharmacy Refill Adherence

### Data Collection

Sites were asked to collect PR records for each prescribed ARV for the entire observation period 6 months prior to and including the baseline visit date. Depending on the site, gathering this information included contacting multiple pharmacies and/or the in-clinic pharmacy. For each ARV refill, sites collected drug name, refill date(s), number of prescribed doses per day, number of prescribed units (pills or mL) per prescribed dose, and number of units dispensed. If initiated or discontinued within the 6 month observation period by the clinician, pharmacies provided the date when the ARV was initiated or stopped. Sites also collected data regarding automatic refill use and, if relevant, reasons PR data collection was not performed.

### Medication Coverage Algorithm

Medication availability over a designated observation period prior to the baseline visit was calculated (as a percentage) for each ARV as the ratio of the summed number of days supplied by refills to the total length of the observation period in days prior to baseline. The observation period was modified appropriately by omitting days prior to initiation or after discontinuation of ARVs by the prescribing clinician. More complex scenarios are described in the Supplemental Text. Overall percent ARV availability (hereafter referred to as PR adherence) was calculated by averaging the percent availability across all prescribed ARVs in the regimen.

### Pharmacy Refill Adherence Measures

The medication coverage algorithm was applied to three observation periods, 2, 4, and 6 months preceding the baseline visit. Participants were defined as adherent if the average availability exceeded 90% across the given observation. For participants who had no records of ARV refills, ARV status was confirmed against AMP study databases. Additionally, an ordinal adherence variable with three levels indicating length of adherence was defined as follows: (1) non-adherent over any of the three observation periods, (2) moderate-term adherent (adherent only over the 2- or 4-month, but not the entire 6-month period), and (3) long-term adherent (adherent over 6-month period). Finally, to independently assess the role of moderate-term adherence, a single dichotomous measure was constructed (i.e., 1 if only adherent over 2- or 4-months, 0 otherwise). Excess doses were not considered when constructing these measures.

### Accounting for Carry-over Doses

"Carry-over" was defined as the excess number of available ARV doses resulting from overlapping coverage (i.e., ARVs were picked up before previous coverage ended). An additional set of adherence measures were calculated for each observation period using the medication coverage algorithm by taking carry-over doses into account. Carry-over doses in a given observation period were utilized to cover $\leq 30$ unsupplied days.

### Early Refilling

A dichotomous variable reflecting early refilling was defined for participants who did not use automatic refill services and had at least one excess dose described as "carry-over" within 6 months prior to the baseline visit. While adherence measures with carry-over doses represent increased medication coverage resulting from excess doses to cover unsupplied days, "early refilling" represents whether refills were picked up at least a day earlier than date coverage ended and independent from adherence status (i.e., early refilling and non-adherence were not mutually exclusive).

### 7-Day Recall Self-report Adherence

Caregivers and youth individually completed self-report questionnaires, administered as an interview, about total prescribed ARV doses and doses missed in the preceding 7 days. The percent of prescribed doses reported as missed in the past 7 days was subtracted from 100% to derive percent adherence for each individual ARV medication. Overall adherence was averaged across all prescribed ARVs in the regimen, and calculated separately for youth and caregiver reports. A global 7-day measure of reported adherence was defined as the worse of either the youth or caregiver report within a youth-caregiver dyad. If either the youth or caregiver questionnaire was not administered, the available measure was used. Individuals were defined as adherent when the average reported adherence exceeded 90%.

## Responsibility for Administering ARVs

As part of the 7-day recall adherence questionnaires, youth and caregivers each were asked who was responsible for administering ARVs: (1) caregiver only; (2) youth only; (3) youth and caregiver shared responsibility; or, (4) youth and another individual shared responsibility. An indicator was created to reflect partial or full youth responsibility based on

reports by either the caregiver or youth. If either the youth or caregiver report was not available, partial or full youth responsibility was based on the available respondent.

### CD4% and Viral Load (VL) Measures

CD4% and VL obtained via AMP study chart abstraction closest to and collected within 6 months prior and up to 2 weeks after the baseline visit were used. Participants were defined as having suppressed viral load (SVL) when VL was < 400 copies/mL; participants whose CD4% was ≥ 25% were considered as having higher CD4%.

### Retention

Participants were identified as retained in the study if they completed the follow-up visit for the Memory Sub-study scheduled two years after baseline.

### Statistical Methods

Participant characteristics were summarized overall and by ordinal PR adherence level [non-adherent, moderate-term adherent (only 2- or 4-month but not the entire 6-month coverage period), or longer term adherent (entire 6-month)]; groups were compared across adherence levels using Chi square tests for categorical measures and the Kruskal–Wallis test for age. Agreement between PR and 7-day recall adherence was measured by Kappa statistics. Several sets of analyses were carried out to explore (1) the association between adherence measures and health outcomes (CD4% ≥ 25%, SVL), and (2) the association among PR and 7-day adherence measures. Associations between adherence measures and study retention were also explored as were those between early refilling and health outcomes. In each set of analyses, multivariable logistic regression models were employed to assess associations of predictors and outcomes, considering the following potential covariates as appropriate: age at baseline, female sex, Hispanic ethnicity, black race, automatic refill use, any youth responsibility for administering ARVs, and regimen change within 2-, 4- and 6-months prior to the baseline visit. The first set of analyses also included the following: Assessment of PR observation length and relative roles of PR and 7-day recall adherence (i.e., including a PR and a 7-day measure in the same adjusted model). Covariates included in adjusted models were predictors demonstrating univariable associations (with $p < 0.20$) either with SVL or CD4% ≥ 25%; a core set of predictors (age at baseline visit, female sex, full or partial youth medication responsibility, and regimen change) was included in all multivariable models. Regimen changes reflected a change within the corresponding PR measures (e.g., 6-month observation was adjusted for a regimen change within 6 months prior to baseline); for models with 7-day measures, a regimen change within 2 months was used.

Multivariable logistic regression also was used to explore predictors of adherence, using the same set of covariates noted above. First, multivariable models were used to separately evaluate associations between covariates and each of the 7-day or PR measures. Each PR measure was added in adjusted models to assess strength of individual measures to predict 7-day adherence. Additional analyses for PR adherence were conducted accounting for carry-over doses. Because medication availability using automatic refill may behave differently, an indicator of automatic refill use was included in all models. To evaluate possible effect modification, supplemental stratified analyses were conducted by sex (male/female), age (< 15, ≥ 15 years) and by youth responsibility to administer ARVs (no youth responsibility vs at least partial youth responsibility for administering ARVs) to evaluate differences in adherence associations. Finally, a sensitivity analysis to assess adherence was conducted using fixed effects models accounting for site effect. A two-sided significance level of $p < 0.05$ from Wald statistics was used. SAS v9.4 (SAS Institute, Cary, NC) was used for all analyses.

## Results

### Participant Characteristics

A total of 173 PHIV youth completed the Memory sub-study baseline visit. Fourteen participants were excluded from these analyses: Three were not on ARVs within 6 months prior to baseline visit, four participants' pharmacies were not willing to share the information, and seven had incomplete data. Following a study team review of comments by site interviewers regarding validity of responses reported for the questionnaires, among those included in the study, a total of four 7-day recall reports (three youth reports and one youth and caregiver report) were excluded from analyses involving self-report adherence. Table 1 describes basic demographic and health characteristics for the 159 PHIV participants included in the study by PR adherence level. The study population was of median age 14.8 years, 55% female, primarily black (74%), with 16% Hispanic. The majority had SVL (76%) and/or CD4% ≥ 25% (75%) at the baseline visit. PR adherence did not significantly differ by prescribed ARVs. Among ARV drug classes, nucleoside reverse transcriptase inhibitors (NRTIs) with one or more protease inhibitors (PIs) (57%) and NRTIs with one or more non-nucleoside reverse transcriptase inhibitors (NNRTIs) (22%) were the most commonly prescribed regimens. On average, youth identified as adherent by self-report were slightly older (14.9 years)

**Table 1** Baseline characteristics: pharmacy refill adherence

| Characteristic[a,b] | Total (N = 159) | Non-adherent (N = 53) | Moderate-term adherent (Only 2 or 4 month) (N = 30) | Long-term adherent (6 month) (N = 76) | p Value |
|---|---|---|---|---|---|
| Age at baseline visit Median (Q1, Q3) | 14.8 (12.4, 16.9) | 14.9 (13.0, 17.5) | 15.7 (13.8, 17.5) | 14.0 (11.8, 16.5) | 0.037* |
| Female sex n(%) | 88 (55%) | 29 (55%) | 17 (57%) | 42 (55%) | 0.985** |
| Black race n(%) | 117 (74%) | 40 (75%) | 22 (73%) | 55 (72%) | 0.925** |
| Hispanic ethnicity n(%) | 25 (16%) | 7 (13%) | 5 (17%) | 13 (17%) | 0.826** |
| Drug class ARV regimen grouping | | | | | |
| NRTI + NNRTI + PI n(%) | 17 (11%) | 5 (10%) | 2 (7%) | 10 (13%) | 0.757** |
| NRTI + NNRTI n(%) | 34 (22%) | 8 (16%) | 7 (24%) | 19 (25%) | |
| NRTI + PI n(%) | 88 (57%) | 29 (58%) | 17 (59%) | 42 (55%) | |
| NNRTI + PI n(%) | 5 (3%) | 2 (4%) | 1 (3%) | 2 (3%) | |
| Other ARV n(%) | 11 (7%) | 6 (12%) | 2 (7%) | 3 (4%) | |
| VL < 400 copies/mL n(%) | 112 (76%) | 32 (64%) | 23 (77%) | 57 (85%) | 0.030** |
| CD4% ≥ 25% n(%) | 115 (75%) | 32 (63%) | 24 (80%) | 59 (82%) | 0.042** |
| Retention at follow-up n(%) | 134 (84%) | 37 (70%) | 29 (97%) | 68 (89%) | 0.001** |
| Caregiver 7-day recall n(mean % adherence) | 113 (85%) | 33 (79%) | 20 (83%) | 60 (90%) | 0.287** |
| Youth 7-day recall n(mean % adherence) | 111 (81%) | 31 (67%) | 19 (79%) | 61 (91%) | 0.007** |
| Global 7-day (worst of) n(mean % adherence) | 119 (79%) | 34 (67%) | 22 (81%) | 63 (86%) | 0.029** |
| Any youth ARV responsibility n(%) | 129 (82%) | 45 (85%) | 23 (79%) | 61 (80%) | 0.749** |
| Regimen change in past 6 months n(%) | 20 (13%) | 6 (11%) | 7 (23%) | 7 (9%) | 0.134** |
| Early refilling n(%) | 58 (36%) | 14 (26%) | 15 (50%) | 29 (38%) | 0.092** |
| Automatic refill n(%) | 58 (36%) | 9 (17%) | 7 (23%) | 42 (55%) | < 0.001** |

*VL* viral load, *Q* quartile, *ARV* antiretroviral

[a]Incomplete baseline characteristics with number of missing records: VL < 400 copies/mL [12], CD4% ≥ 25% [6], Caregiver 7-day [26], Youth 7-day [22], Global 7-day [8], Any youth ARV responsibility [1]

[b]Missing records are excluded from p-value calculations

*Kruskal–Wallis Test, **Chi Square Test

compared to youth reported to be adherent by their caregivers (14.4 years) (data not shown). The study retention rate was fairly high; only 25 (16%) participants did not complete the follow-up visit.

## Adherence Measures

### Pharmacy Refill

Adherence by PR ranged from 48 to 62%, depending on the time period considered, with shorter observation periods exhibiting higher adherence levels. The number of participants who were not adherent for any observation period was 53 (33%); fewer participants were moderate-term adherent (19%) compared to those who were longer-term adherent (48%). When allowing for carry-over, adherence increased slightly to 50–65% (Fig. 1). A higher percentage of adherent participants had SVL or CD4% ≥ 25% compared to non-adherent youth; when assessed over the levels of the ordinal PR measure, a pattern for likelihood of better health was observed (SVL: non-adherent over any observation, 64%; moderate-term adherent, 77%; and, long-term adherent, 85%). Participants who were longer-term adherent were significantly younger (median age, 14 years) than those who were non-adherent or moderate-term adherent (Table 1). The use of automatic refills was significantly higher for adherent than non-adherent participants (55 vs. 19% for 6-month coverage period); baseline automatic refill use did not differ significantly by participant demographics or health characteristics but was slightly higher among participants who completed the follow-up visit (data not shown).

### 7-Day Recall

Caregiver-reported recall adherence was 85% while youth self-reported recall adherence was 81%. Global 7-day

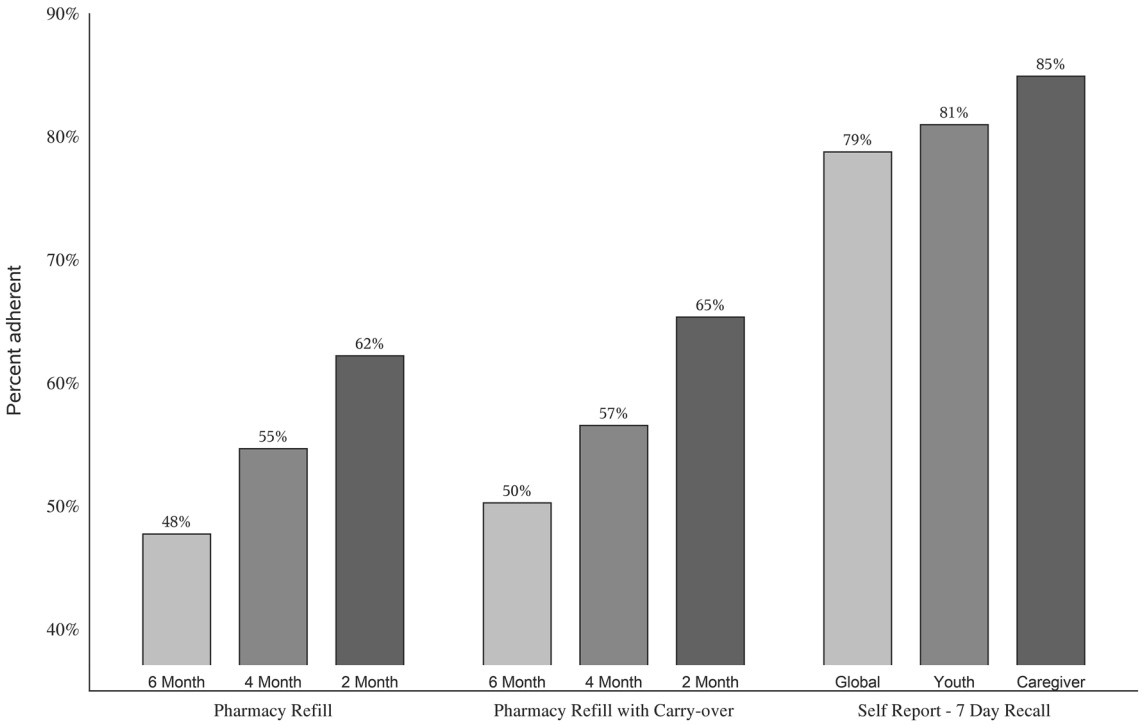


**Fig. 1** Percent of adherent participants by adherence measure

adherence (worse of caregiver or youth report in dyad, n = 152) was 79% (Fig. 1). Associations of 7-day recall with the ordinal PR measure exhibited a pattern similar to that for SVL, showing higher 7-day adherence with more consistent PR adherence (youth report: non-adherent over any pharmacy-refill observation, 67%; moderate-term, 79%; and, long-term, 91%; Table 1).

### Adherence and Health Outcome Models

In multivariable models, significant positive associations were found for each PR measure with CD4% ≥ 25% and SVL, after adjusting for age at baseline visit, female sex, full or partial youth medication responsibility, and regimen change, as illustrated in Fig. 2. Adjusted odds ratios (ORs) for associations were similar for caregiver- and self-reported 7-day recall. Similar significant results were observed with the ordinal PR measure; each categorical increase (non-adherence to moderate-term adherence to longer-term adherence) had OR 2.12 (95% CI (1.25, 3.60)) for SVL and OR 1.92 (95% CI (1.15, 3.23)) for CD4% ≥ 25%. Among 7-day recall measures, caregiver-reported adherence showed the strongest association with both CD4% ≥ 25% (OR 7.69 CI (2.43, 24.34)) and SVL (OR 4.49 CI (1.47, 13.79)). Among PR measures, associations were strongest with the 2-month measure accounting for carry-over doses (SVL: OR 4.90 CI (1.95, 12.32)). PR measures accounting for carry-over doses demonstrated slightly stronger associations with CD4% ≥ 25% and SVL compared to those that did not (Fig. 2). Similar results were observed in sensitivity analyses accounting for sites as fixed effects (data not shown).

When long-term (6-month) and moderate-term adherence measures were included in the same adjusted model, OR estimates for the association with SVL were roughly comparable to levels corresponding to models including the ordinal measure alone. When both ordinal and a 7-day measure were used in same model, estimates for the ordinal measure remained the same; however, associations for the 7-day measures were weaker compared to models using a single adherence measure (Table 2).

When associations between PR adherence measures and clinical outcomes were evaluated separately by sex, age, and medication responsibility, we observed slightly stronger associations for females and for younger participants. Stratifying by youth responsibility for administering medications was difficult to interpret due to the small number of youth who were not at all responsible for their ARVs resulting in wide confidence intervals. However, when including youth at least partially responsible for their ARVs, despite observed wider confidence intervals, associations were generally in the same direction and of a similar magnitude supporting our original findings noted above (data not shown).

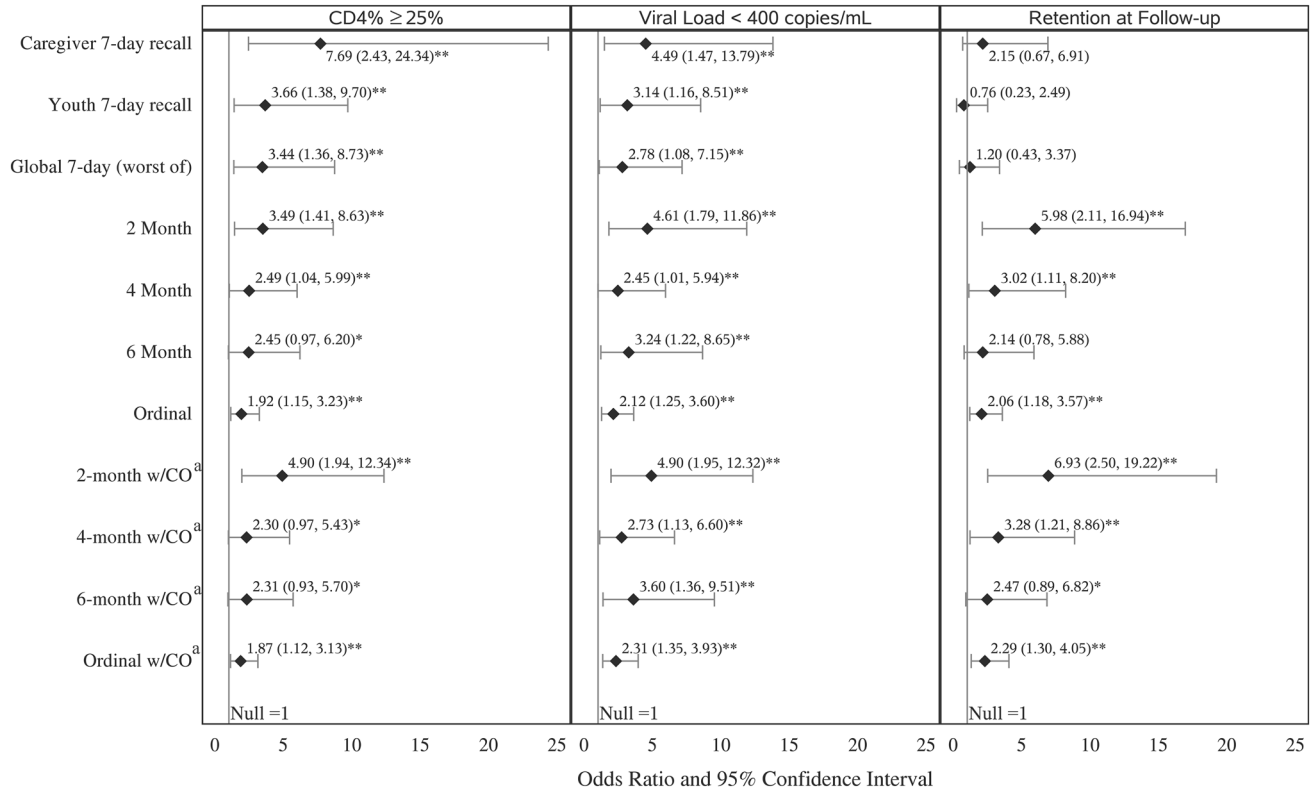


**Fig. 2** Adjusted associations of adherence estimates with primary and secondary outcomes. CO = carry-over doses, *Marginal statistical significance ($0.05 \leq p < 0.1$). **Statistical significance ($p < 0.05$). [a]Pharmacy refill measure accounts for carry-over doses

**Table 2** Adjusted odds ratio estimate of multiple adherence measures when included in same model to predict health outcomes

| Measures included | Moderate-term[a] adherent | Long-term[b] adherent | Ordinal | 7-day recall |
|---|---|---|---|---|
| Outcome = VL < 400 | | | | |
| Moderate[a] + long-term[b] | 2.55 (0.81, 8.02) | 4.47 (1.55, 12.91)** | | |
| Ordinal + caregiver | | | 2.12 (1.13, 3.97)** | 3.26 (1.01, 10.55)** |
| Ordinal + youth | | | 2.13 (1.16, 3.92)** | 1.94 (0.66, 5.74) |
| Ordinal + global | | | 2.14 (1.20, 3.81)** | 2.17 (0.81, 5.79) |
| Outcome = CD4% ≥ 25% | | | | |
| Moderate[a] + long-term[b] | 3.12 (0.98, 9.99)* | 3.62 (1.31, 9.99)** | | |
| Ordinal + caregiver | | | 1.86 (0.99, 3.49)* | 7.31 (2.12, 25.15)** |
| Ordinal + youth | | | 1.73 (0.98, 3.07)* | 2.87 (1.01, 8.17)** |
| Ordinal + global | | | 1.64 (0.94, 2.86)* | 2.93 (1.10, 7.86)** |

[a]Only 2 or 4-month adherent

[b]6-month adherent

*Marginal statistical significance ($0.05 \leq p < 0.1$)

**Statistical significance ($p < 0.05$)

### Associations and Agreement Between Pharmacy Refill and 7-Day Recall Adherence

Results from adjusted logistic regression analyses showed that PR was highly predictive of 7-day recall measures, with the strongest associations for youth-reported 7-day recall, OR 7.61 (2.43, 23.86). Longer observation periods (4- and 6-month) had stronger associations with 7-day recall than 2-month PR measures. Accounting for carry-over doses increased the magnitude of associations with 7-day recall measures. Here, the ordinal measure had significant associations with 7-day measures; highest was with youth report

when carry-over doses were used (OR 3.03 [1.65, 5.59]). Agreement between PR adherence and 7-day recall adherence was weak (Kappa = 0.09–0.25); the highest Kappa values were for youth-reported 7-day recall and 2- and 4-month PR with carry-over doses. Agreements and associations among measures were slightly higher across the three observation periods when carry-over doses were considered (Table 3).

### Baseline Adherence and Retention at Follow-Up Visit

PR for 2- and 4-month measures had significant positive associations with retention at the follow-up visit, while the association with 6-month adherence was weaker. In contrast, none of the associations between retention and 7-day recall measures were significant (Fig. 2).

#### Early Refilling

Early refilling was observed for 58 participants (36%). In general, these youth tended to exhibit better health status markers than those who did not pick up their ARVs early (SVL = 88% vs. 69%, data not shown). In adjusted models, early refilling had strong associations with SVL (OR = 3.89 [1.27, 11.90]) (data not shown).

### Covariates

Covariates were evaluated in models predicting health outcomes as well as adherence measures. A recent regimen change prior to baseline visit (2, 4 or 6 months) showed significant negative associations with CD4% ≥ 25% in all 7-day recall, and in 2- and 4-month PR models; similar significant associations (OR 0.20) were only present in caregiver-reported 7-day recall models for SVL. Females were observed to have significantly higher risk for uncontrolled VL (≥ 400 copies/mL) and lower CD4% (< 25%) in both caregiver and global 7-day models. Among the models with PR predicting 7-day recall adherence, female sex demonstrated weak but positive associations with youth-reported adherence when the 4-month PR measure was used. Older youth age emerged as a risk factor for lower CD4%, which showed at least borderline significance across all models except those using caregiver reported adherence. Older youth age also was found to be a significant risk factor for poorer 4- and 6-month PR adherence while no other adherence measures, including 7-day recall, exhibited associations with age (Supplemental Table I).

## Discussion

Clinicians and researchers alike rely on the availability of valid and feasible adherence measures to understand factors that contribute to poor adherence among youth with HIV and to assess the effectiveness of adherence interventions. Due to known limitations associated with the validity of self-reported adherence, and cost and feasibility issues surrounding electronic adherence monitoring, we explored the characteristics of PR adherence measures and their performance in predicting clinical outcomes in youth with PHIV using data from the PHACS Memory sub-study. PR adherence measures showed strong associations with SVL and CD4% ≥ 25%, comparable to 7-day recall measures, consistent with results in previously reported adult HIV studies.

**Table 3** Adjusted associations and agreements between pharmacy refill and 7-day adherence measures

| | Caregiver 7-day recall | | | Youth 7-day recall | | | Global (worst of) | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | Kappa | N | OR (95% CI) | Kappa | N | OR (95% CI) | Kappa | N |
| Pharmacy refill | | | | | | | | | |
| 2-Month | 3.06 (0.98, 9.53)* | 0.10 | 133 | 4.10 (1.50, 11.21)** | 0.20 | 137 | 3.13 (1.23, 7.95)** | 0.16 | 147 |
| 4-Month | 3.47 (1.12, 10.76)** | 0.10 | 133 | 7.61 (2.43, 23.86)** | 0.23 | 137 | 4.18 (1.56, 11.19)** | 0.16 | 147 |
| 6-Month | 3.81 (1.18, 12.28)** | 0.09 | 133 | 6.41 (2.02, 20.28)** | 0.19 | 137 | 3.51 (1.31, 9.42)** | 0.13 | 147 |
| Ordinal | 2.02 (1.09, 3.75)** | NA[a] | 133 | 2.75 (1.53, 4.97)** | NA[a] | 137 | 2.15 (1.26, 3.65)** | NA[a] | 147 |
| With carry-over | | | | | | | | | |
| 2-Month | 3.55 (1.16, 10.89)** | 0.13 | 133 | 4.93 (1.82, 13.31)** | 0.25 | 137 | 3.71 (1.48, 9.30)** | 0.20 | 147 |
| 4-Month | 3.62 (1.17, 11.17)** | 0.11 | 133 | 7.96 (2.56, 24.76)** | 0.25 | 137 | 4.38 (1.65, 11.63)** | 0.18 | 147 |
| 6-Month | 4.30 (1.28, 14.45)** | 0.10 | 133 | 7.12 (2.19, 23.13)** | 0.21 | 137 | 3.80 (1.40, 10.33)** | 0.14 | 147 |
| Ordinal | 2.24 (1.17, 4.31)** | NA[a] | 133 | 3.03 (1.65, 5.59)** | NA[a] | 137 | 2.34 (1.35, 4.05)** | NA[a] | 147 |

*OR* odds ratio, *CI* confidence interval, *NA* not applicable

[a]Kappa is not calculated to assess agreements between ordinal and 7-day recall measures

*Marginal statistical significance ($0.05 \leq p < 0.1$)

**Statistical significance ($p < 0.05$)

These results support the use of PR measures to evaluate youth adherence, and suggest the adherence pattern observed in PR records may illuminate true adherence behaviors in a cost-effective manner. By evaluating shorter to longer observation periods, we demonstrated that PR measures have the ability to capture temporal fluctuations in adherence behaviors. Additionally, examining carry-over doses identified early refilling behavior, which was associated with better HIV health status indicators. Finally, baseline PR adherence was predictive of study retention 2 years after baseline, suggesting PR adherence and adherence to appointments may involve related underlying health behaviors.

A key strength of this study was the systematic evaluation of PR measures across three observation periods (2-, 4-, 6-month), and accounting for carry-over doses. Although varied, consistently strong associations between adherence and health outcomes were found for all observation periods, and were slightly stronger when accounting for carry-over doses. Among the three observation periods, the 2-month observation window demonstrated the strongest performance. This may be in part because the majority of VL and immunologic data were obtained a few weeks prior to the baseline visit, thus strengthening the associations due to temporal proximity in data collection. Although the strongest relationships were found for 2-month refills, results also suggested long-term adherent participants had better health outcomes and a higher likelihood of reporting 7-day adherence compared to moderate-term adherers. Increased PR adherence over a 2-month observation prior to the baseline visit may, similar to 7-day measures, reflect a true increase in adherence as the clinic visit approaches, when youth may have started receiving visit reminder calls and know they are going to be asked how well they have been taking their medications and/or that their VL will be measured. On the other hand, when looked at ordinally, better health outcomes and 7-day recall adherence were each associated with longer-term compared to moderate-term PR adherence, outcomes which could be explained by consistent use of medication over the longer term. Regardless, the three-level ordinal PR adherence based on multiple observation lengths was found to be predictive of health outcomes for PHIV youth. Future use of this assessment method would not only allow researchers to study barriers to poor adherence but also to explore features associated with and to understand the impact of "moderate-term" adherence on clinical and health outcomes.

While informative, PR measures unfortunately are not perfect. They represent medication availability and as a result may overestimate true adherence. Regardless, any shortcoming does not override the utility, accuracy, and convenience of PR-measured adherence presented herein. Levels of the ordinal measure, from non-adherent to moderate-term adherent and to long-term adherent, identified patterns for improved health and higher likelihood of 7-day adherence which may help researchers and healthcare providers gain additional insight into adherence behaviors. While agreement between PR and 7-day adherence measures was weak, both were predictive of health outcomes and, as such, this may suggest that each method truly assesses different aspects of adherence behaviors, such as planning, organizing, and remembering to take medication, which may be tapped into differently by PR and self- or caregiver-reported adherence. Nonetheless, our findings suggest the additional utility of PR records to understand disease severity in PHIV youth.

An additional utility of pharmacy refill records is to model the effect of early refilling. While it creates a measurement challenge, early refilling may be considered an indicator of persistence in taking medication. Participants who appear motivated to pick up refills early may be more stringent adherers to prescribed ARVs and assure they do not miss a dose by always having medication on hand. Our results show that early refilling was associated with better health. The impact of early refilling needs to be further explored in a larger study.

Interestingly, female adolescents were at significantly greater risk for unsuppressed VL and lower CD4% compared to males when youth self-reported adherence was used. To the contrary, being female was not significant for PR results suggesting a potential over-reporting response bias by females on the 7-day recall measure. This finding alone emphasizes the importance of using more objective adherence measures, especially when the validity of self-report questionnaires may differ by gender, be subject to social desirability, and affect treatment decisions. PR measures also captured deteriorating adherence with increasing age which was not evident by 7-day adherence reports. Four- and 6-month observation periods were more effective in identifying differing adherence patterns for older youth who are more likely to have fluctuations in their adherence over time.

As youth with PHIV age up, study retention becomes an important factor for researchers who have followed these youth since birth. Our results show that baseline PR measures were predictive of study retention at the follow-up visit 2 years later. Among PR measures, the 2-month measure was the strongest predictor, suggesting that the factors associated with better adherence nearer to the study visit may be similar to those associated with study retention. Researchers and health care providers can utilize PR measures to help identify participants at risk for loss-to-follow-up and provide custom interventions to keep them on study and/or in care. Our results also confirm that adherence to ARVs, study retention, and similarly retention in HIV clinical care, should be considered collectively especially as PHIV youth transition to adult care. Potential causal links between adherence and retention should be further explored in longitudinal studies for youth with PHIV.

This study is not without limitations. First, the sample was relatively healthy and results may not generalize to all youth with PHIV, or youth with PHIV who otherwise do not participate in research. Pharmacy data were retrospective and cross-sectional and thus did not allow for the exploration of time-dependent factors. Finally, a very small number of viral load and CD4 measurements were obtained 4 to 6 months prior to the baseline visit, which may have attenuated associations with the 2-month adherence measure.

In summary, all three PR adherence observation windows, with or without carry-over assumptions, showed strong associations with HIV disease status markers confirming that PR methods are viable, appropriate alternative adherence assessment strategies. This finding may be particularly useful in behavioral and neurocognitive research for youth with PHIV when there is a concern about validity of self-report due to memory impairment or other factors. Overall, our findings on PR adherence confirm that assessing youth adherence to ARVs is more complex than simply dichotomously defining as adherent vs non-adherent. Adding questions about PR behaviors to self-report questionnaires might prove beneficial. Such questions might include asking about non-adherence (never/rarely picks up refills on time), moderate-term adherence (sometimes leaves gaps between refills) vs long-term adherence (never/rarely leaves gaps between refills), early refilling (plans and organizes ahead of time to pick up on time or a few days prior to running out of medication), or carry-over doses (when refills ARVs earlier and keeps excess doses for future use), although these would still be subject to response bias as is any self-report.

In conclusion, our study findings emphasize the value of using PR measures, especially with varied observation periods, to better understand dynamic adherence behaviors in youth with PHIV. Comparison of alternate measures of adherence has been recommended by others in the field [6]. PR measures appear to be an appropriate option to use in combination with self-report and/or electronic monitoring in both research and clinical contexts. Availability of a standardized PR data collection process that can be implemented across pharmacies would be helpful to easily code and implement the medication coverage algorithm (as provided in Supplemental Text) for a wider, practical use of pharmacy refill data.

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## Compliance with Ethical Standards

**Conflict of interest** All authors declare that they have no conflicts of interest to report.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## References

1. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to

test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011;52(6):793–800.
2. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. AIDS Patient Care STDs. 2014;28(3):128–35.
3. Neilan AM, Karalius B, Patel K, Van Dyke RB, Abzug MJ, Agwu AL, et al. Association of risk of viremia, immunosuppression, serious clinical events, and mortality with increasing age in perinatally human immunodeficiency virus-infected youth. JAMA Pediatr. 2017;171(5):450–60.
4. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. Curr HIV/AIDS Rep. 2009;6(4):194–200.
5. Kacanek D, Angelidou K, Williams PL, Chernoff M, Gadow KD, Nachman S, et al. Psychiatric symptoms and antiretroviral nonadherence in US youth with perinatal HIV: a longitudinal study. Aids. 2015;29(10):1227–37.
6. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management. Pediatrics. 2007;119(6):e1371–83.
7. Williams PL, Storm D, Montepiedra G, Nichols S, Kammerer B, Sirois PA, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. Pediatrics. 2006;118(6):e1745–57.
8. Buchanan AL, Montepiedra G, Sirois PA, Kammerer B, Garvie PA, Storm DS, et al. Barriers to medication adherence in HIV-infected children and youth based on self- and caregiver report. Pediatrics. 2012;129(5):e1244–51.
9. Ingerski LM, Hente EA, Modi AC, Hommel KA. Electronic measurement of medication adherence in pediatric chronic illness: a review of measures. J Pediatr. 2011;159(4):528–34.
10. van den Boogaard J, Lyimo RA, Boeree MJ, Kibiki GS, Aarnoutse RE. Electronic monitoring of treatment adherence and validation of alternative adherence measures in tuberculosis patients: a pilot study. Bull World Health Organ. 2011;89(9):632–9.
11. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. J Acquir Immune Defic Syndr. 2006;43(Suppl 1):S79–87.
12. Williams AB, Amico KR, Bova C, Womack JA. A proposal for quality standards for measuring medication adherence in research. AIDS Behav. 2013;17(1):284–97.
13. Usitalo A, Leister E, Tassiopoulos K, Allison S, Malee K, Paul ME, et al. Relationship between viral load and self-report measures of medication adherence among youth with perinatal HIV infection. AIDS Care. 2014;26(1):107–15.
14. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med. 2015;5(4):470–82.
15. Wagner G. Utility of self-reported antiretroviral adherence: comment on Simoni et al. (2006). AIDS Behav. 2006;10(3):247–8.
16. Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. Ann Pharmacother. 2009;43(3):413–22.
17. Farley J, Hines S, Musk A, Ferrus S, Tepper V. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. J Acquir Immune Defic Syndr. 2003;33(2):211–8.
18. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother. 2006;40(7–8):1280–8.
19. Grossberg R, Gross R. Use of pharmacy refill data as a measure of antiretroviral adherence. Curr HIV/AIDS Rep. 2007;4(4):187–91.
20. Andrade AS, Deutsch R, Duarte NA, Marcotte TD, Umlauf A, et al. Relationships among neurocognitive status, medication adherence measured by pharmacy refill records, and virologic suppression in HIV-infected persons. J Acquir Immune Defic Syndr. 2013;62(3):282–92.
21. Lehmann A, Aslani P, Ahmed R, Celio J, Gauchet A, Bedouch P, et al. Assessing medication adherence: options to consider. Int J Clin Pharm. 2014;36(1):55–69.
22. Sangeda RZ, Mosha F, Prosperi M, Aboud S, Vercauteren J, Camacho RJ, et al. Pharmacy refill adherence outperforms self-reported methods in predicting HIV therapy outcome in resource-limited settings. BMC Public Health. 2014;14:1035.
23. Zogg JB, Woods SP, Weber E, Iudicello JE, Dawson MS, Grant I, et al. HIV-associated prospective memory impairment in the laboratory predicts failures on a semi-naturalistic measure of health care compliance. Clin Neuropsychol. 2010;24(6):945–62.
24. Albert SM, Weber CM, Todak G, Polanco C, Clouse R, McElhiney M, et al. An observed performance test of medication management ability in HIV: relation to neuropsychological status and medication outcomes. AIDS Behav. 1999;3:121–8.
25. Ettenhofer ML, Foley J, Castellon SA, Hinkin CH. Reciprocal prediction of medication adherence and neurocognition in HIV/AIDS. Neurology. 2010;74(15):1217–22.
26. Hinkin CH, Castellon SA, Durvasula RS, Hardy DJ, Lam MN, Mason KI, et al. Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. Neurology. 2002;59(12):1944–50.
27. Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. Aids. 2004;18(Suppl 1):S19–25.
28. Thames AD, Arentoft A, Rivera-Mindt M, Hinkin CH. Functional disability in medication management and driving among individuals with HIV: a 1-year follow-up study. J Clin Exp Neuropsychol. 2013;35(1):49–58.
29. Wolf MS, Curtis LM, Wilson EA, Revelle W, Waite KR, Smith SG, et al. Literacy, cognitive function, and health: results of the LitCog study. J Gen Intern Med. 2012;27(10):1300–7.
30. Waldrop-Valverde D, Guo Y, Ownby RL, Rodriguez A, Jones DL. Risk and protective factors for retention in HIV care. AIDS Behav. 2014;18(8):1483–91.
31. de Boer IM, Prins JM, Sprangers MA, Nieuwkerk PT. Using different calculations of pharmacy refill adherence to predict virological failure among HIV-infected patients. J Acquir Immune Defic Syndr. 2010;55(5):635–40.
32. Saberi P, Caswell N, Amodio-Groton M, Alpert P. Pharmacy-refill measure of adherence to efavirenz can predict maintenance of HIV viral suppression. AIDS care. 2008;20(6):741–5.
33. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. J Clin Epidemiol. 2004;57(10):1107–10.
34. Acri TL, Grossberg RM, Gross R. How long is the right interval for assessing antiretroviral pharmacy refill adherence? J Acquir Immune Defic Syndr. 2010;54(5):e16–8.
35. Abah IO, Ojeh VB, Musa J, Ugoagwu P, Agaba PA, Agbaji O, et al. Clinical utility of pharmacy-based adherence measurement in predicting virologic outcomes in an adult HIV-infected cohort in Jos, North Central Nigeria. J Int Assoc Provid AIDS Care. 2016;15(1):77–83.
36. Ernesto AS, Lemos RM, Huehara MI, Morcillo AM, Dos Santos Vilela MM, Silva MT. Usefulness of pharmacy dispensing records in the evaluation of adherence to antiretroviral therapy in Brazilian children and adolescents. Braz J Infectious Dis. 2012;16(4):315–20.

37. Marhefka SL, Farley JJ, Rodrigue JR, Sandrik LL, Sleasman JW, Tepper VJ. Clinical assessment of medication adherence among HIV-infected children: examination of the Treatment Interview Protocol (TIP). AIDS Care. 2004;16(3):323–38.
38. Katko E, Johnson GM, Fowler SL, Turner RB. Assessment of adherence with medications in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2001;20(12): 1174–6.