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Adherence and Viral Suppression among Infants and Young Children Initiating Protease Inhibitor-Based Antiretroviral Therapy

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Abstract

Background—High levels of adherence to antiretroviral therapy (ART) are considered necessary to achieve viral suppression. We analyzed data from a cohort of HIV-infected children who were less than 2 years of age receiving protease inhibitor (PI)-based ART to investigate associations between viral suppression and adherence ascertained using different methods.

Methods—Data were from the pre-randomization phase of a clinical trial in South Africa of HIV-infected children initiating either ritonavir-boosted lopinavir (LPV/r)- or ritonavir-based ART. At scheduled visits during the first 24 weeks of enrollment, study pharmacists measured quantities of medications returned (MR) to the clinic. Caregivers answered questionnaires on missed doses and adherence barriers. Associations between adherence and viral suppression (HIV-1 RNA <400 copies/mL) were investigated by regimen.

Results—By 24 weeks, 197/269 (73%) children achieved viral suppression. There was no association between viral suppression and caregiver reported missed doses or adherence barriers. For children receiving the LPV/r-based regimen, MR adherence to each of the three drugs in the regimen (LPV/r, lamivudine or stavudine) individually or together was associated with viral suppression at different adherence thresholds. For example, <85% adherence to any of the three medications significantly increased odds of lack of viral suppression (Odds Ratio [OR] 2.30 [95% CI: 1.30–4.07], p=.004). In contrast, for children receiving the ritonavir-based regimen, there was no consistent pattern of association between MR and viral suppression.

Conclusions—Caregiver reports of missed doses did not predict virologic response to treatment. Pharmacist medication reconciliation correlated strongly with virologic response for children taking a LPV/r-based regimen and appears to be a valid method for measuring pediatric adherence.

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Authors' contributions

EJA, AC, RS, LM and LK participated in study design, ethical clearance and data collection. CT and LK participated in data analysis. All authors read and approved the final manuscript.

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Keywords

adherence; pediatric ART; HIV; measurement

There are an estimated 3.4 million children less than 15 years of age living with HIV/AIDS worldwide, 90% of whom live in sub-Saharan Africa.[1] Care and treatment services for children living with HIV in resource-limited settings have expanded in recent years.[1] The use of ART has demonstrated great success in reducing morbidity and mortality in children with HIV.[2,3] In pooled data from cohorts across sub-Saharan Africa, 70% of children were found to have viral suppression after 12 months on ART (95% CI, 67%–73%) with mortality at 12 months across 11 studies, ranging from 0.0% to 18.8%.[4]

Once a child starts ART, adherence to antiretroviral medications is critical for achieving and maintaining successful clinical, virologic and immunologic outcomes. Adherence, defined as taking all prescribed medication doses, is arguably *the* most important parameter for successful outcomes of HIV treatment.[5] In HIV-infected adults on ART,<95% adherence is associated with decreased CD4 cell response,[6] increased risk of virologic failure[7] and increased mortality,[8] however, these effects may be modified by the timing of non-adherence[9] and regimen type, i.e. non-nucleoside reverse transcriptase inhibitor (NNRTI) versus protease inhibitor (PI)-based ART.[10]

Less is known about optimal adherence levels and dynamics of viral suppression in children, particularly young children and those in less developed countries. A small number of studies have estimated optimal adherence levels for predicting viral suppression in children ranging from ≥80% in a Zambian cohort[11] to ≥90% from studies in South Africa[12] and the United States.[13] The impact of adherence on treatment outcomes in children may also vary by timing of non-adherence and regimen type although few studies have examined these issues specific to pediatric patients. A small study from South Africa found that children taking boosted PI-based regimens could achieve viral suppression with lower levels of adherence than children taking NNRTI-based regimens.[14]

Effective monitoring of adherence poses challenges, especially in children. The simplest and least expensive method uses structured questionnaires to assess number of missed doses as reported by caregivers of young children. Questionnaires about barriers to adherence, such as the caregiver forgetting to give medication or the child refusing to take the treatment, have also been developed for assessing adherence in clinical trials.[15] Pill counts of returned medication, or weights of returned syrups for young children, can also be used to estimate the percentage of doses taken. Unannounced pill counts[16] and electronic pill cap monitoring systems (MEMS)[17] are considered the gold standard; however, these methods are complex and expensive and may not be feasible outside of research settings.[18]

MATERIALS AND METHODS

We conducted a secondary analysis of data collected during the pre-randomization phase of an ART strategies trial conducted at a single site in Johannesburg, South Africa. The trial was designed to evaluate the reuse of nevirapine in exposed HIV-infected children and is described in detail elsewhere.[19,20] In brief, HIV-infected children between the ages of 6 and 104 weeks of age with peri-partum nevirapine exposure who were ART-naïve and eligible to initiate ART, were screened for the trial between 2005 and 2007. Children who had initiated ART within the previous year and were otherwise eligible were also enrolled. Children were followed from treatment initiation (or enrollment if already on treatment) until they reached and sustained viral suppression (<400 copies/mL) and were randomized, or until they were

lost to follow-up, died or to 52 weeks post enrollment if they did not achieve viral suppression. Pre-randomization clinical outcomes have been previously reported.[21,22] Caregivers of enrolled children gave written informed consent. The study received ethics approval from the Institutional Review Boards at Columbia University (New York, NY) and the University of Witwatersrand (Johannesburg, South Africa).

The ART regimen for children older than six months and not on tuberculosis (TB) treatment was ritonavir-boosted lopinavir (LPV/r), stavudine and lamivudine twice daily. For children younger than 6 months of age and those receiving co-treatment for TB, ART consisted of ritonavir, stavudine and lamivudine twice daily. When children completed TB treatment or reached six months of age, LPV/r was substituted for ritonavir. All study drug regimens were in line with South African pediatric ART guidelines at the time.[23] After enrollment children were seen at weeks 2, 4, 8, 12 and every 3 months thereafter for clinical and laboratory monitoring, including CD4 and viral load testing (HIV RNA quantification range 400–750,000 copies/mL; Roche Amplicor).

Adherence to treatment was assessed at each scheduled visit using a structured questionnaire administered to the caregiver. The adherence instrument was adapted from the Pediatric AIDS Clinical Trials Group (PACTG) questionnaire[15] and included caregiver reports of six specific adherence barriers: child uncooperative, child refusing medication, child spitting up or vomiting medication, caregiver forgetting to give medication, caregiver fears of side effects and caregiver not wanting others to see child taking medication. Caregivers were asked to report (1) how many doses of each prescribed drug had been given on the day prior to the study visit and (2) when the child last missed a dose of any prescribed drug (which drug missed was not specified).

Caregivers were also required to return all medication containers, either syrup bottles (LPV/r and lamivudine) or pill containers (stavudine), and any unused medication. At scheduled visits, the study pharmacist weighed remaining syrup in returned bottles and counted returned pills. Medication return (MR) percentages were calculated for each drug by dividing the estimated actual usage (based on the amount prescribed at the previous visit minus the amount returned) by the expected drug usage multiplied by 100. For example, for a child who was prescribed 35 tablets and expected to take 30, if the caregiver returned 10 tablets, the estimated actual usage was 25, which was divided by the expected usage of 30 and would equal a medication return of 83% (25/30×100). If the caregiver returned 2 tablets of the 35 prescribed, the estimated actual usage was 33 tablets and the medication return percentage was calculated to be 110% (33/30×100). All percentages greater than 100% were considered fully adherent.

To categorize adherence based on MR, cutoffs ranging from 60% to 99% were created using the continuous medication return percentages. MR percentages of equal to or more than the cutoff percent were coded as adherent, while a lower MR percentage than the cutoff value was considered non-adherent. For MR percentages of >100% (indicating greater than expected usage), a value of 100% MR adherence was imputed. For each visit with at least one MR, the most non-adherent MR was identified and classified according to the adherence cutoffs (“largest MR”). Average adherence to each drug was calculated for all subjects using all MRs for the subject through 24 weeks of follow-up (excluding missing returns). Mean overall adherence to each antiretroviral drug was calculated using the subject average adherence. Medications not brought to scheduled visits were recorded as missing

Children with at least one visit with caregiver report of adherence, MR assessment and viral load measurement, as well as follow-up to ≥24 weeks were included in the analysis.

The outcome for this analysis was viral suppression of <400 copies/mL by 24 weeks follow-up. Children who achieved a viral load of <400 copies/mL at any visit from enrollment through the 24 week study visit were considered to have achieved viral suppression even if they had a subsequent viral load ≥400 copies/mL. Those who only achieved suppression after 24 weeks were considered not suppressed.

Statistical Analysis

We evaluated three types of adherence measures as predictors of viral suppression: reported adherence barriers, reported missed doses and MR. We examined the frequency of non-adherence at all visits up to 24 weeks for the entire cohort and among children who did and did not achieve viral suppression. Logistic regression modeling with generalized estimating equations (GEE) (accounting for multiple subject observations) with an exchangeable correlation matrix was used to evaluate the relationship between adherence measures and viral suppression. Analysis was stratified by regimen (LPV/r- or ritonavir-based) at the visit. Baseline subject characteristics were assessed as independent predictors of suppression in logistic models. Subject characteristics were also modeled as predictors of adherence in logistic GEE models, using the MR cutoffs most strongly associated with viral suppression as the adherence endpoint. The agreement between MR and reported missed doses was assessed with kappa statistics. All statistical procedures were conducted using SAS (version 9.1.3, SAS Institute).

RESULTS

Of the 341 children enrolled in the study, 9 (3%) died and 9 (3%) were lost to follow-up before the first study visit. 323 children initiated treatment, 254 (79%) as part of the study and 69 prior to enrollment. Of 323 children, 31 (11%) died, 22 (7%) were lost to follow-up, and one child (0.3%) did not have any visits with reported adherence within the first 24 weeks of follow-up.

There were 269 children included in this analysis with a total of 1351 scheduled visits up to and including the 24 week study visit. The mean number of visits per child was 5 (range 3–6). Overall, 125 (46%) of the 269 children received a LPV/r-based regimen; 50 (19%) were on a ritonavir-based regimen and 94 (35%) received both regimens, at different stages, over the first 24 weeks of study. Enrollment characteristics have been described elsewhere[21,22]. Briefly, 175 of 269 children (65%) were <12 months of age at enrollment; the median age was 9.2 months. The mean CD4 percentage was 18.7%, 141 of 236 children (60%) had pre-treatment viral loads ≥750,000 copies/mL and 208 children (77%) were WHO stage 3 or 4 at enrollment. Among the 144 children who were on a ritonavir-based regimen during the first 24 weeks of follow-up, 68 (47%) were six months of age or younger at enrollment and 76 (53%) were on TB treatment at the time of ART initiation or during follow-up. The biological mother was the primary caretaker for 254 (94%) children. Most reported having electricity in the home (84%), while fewer than half reported a tap (44%) or indoor toilet (37%).

Of the 269 children included in this analysis, 197 (73%) achieved viral suppression by week 24 of follow-up. As previously reported[21], pre-treatment viral load was significantly higher among children who did not suppress by this time (p=0.005). Non-suppressed children were also more likely to have been treated for TB (p=0.03). Those children treated with ritonavir were also significantly less likely to suppress (p<0.00001)[21]. Of 269 subjects, 23 (9%) missed one or more scheduled visits and missing a visit was significantly associated with failure to suppress (p=0.002).

Adherence barriers

Adherence barriers reported at each visit up to 24 weeks are shown in Table 1. At least one barrier to adherence was reported at 419 (35%) visits and ever reported by 203 (76%) caregivers. The most commonly reported barrier was that the child was uncooperative. There were more barriers reported at visits with children on ritonavir-based regimens (39%) compared with LPV/r-based regimen visits (33%) (p=0.03) (Table 1). There were no significant differences in reports of adherence barriers between children who suppressed and those who did not.

Missed doses

Reports of missed doses were infrequent; there were only 94 visits of 1351 (8%) in which a missed dose of medication was reported (Table 1). There were slightly fewer reports of missed doses at visits with children on the ritonavir-based regimen (6%) compared with children on the LPV/r-based regimen (9%) (p=0.05). Report of incorrect dosage of any drug was also infrequent and was reported at<1% of all visits (Table 1). There was no significant difference in reports of missed or incorrect doses between suppressed and non-suppressed children.

Medication return

Average adherence to LPV/r as measured by MR was 97% (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B419). Suppressed children had higher average LPV/r adherence than non-suppressed children, 98% versus 95% (p=0.04). The lowest average adherence to any drug was found for ritonavir which was 95% for 140 children with MR of this drug. Average ritonavir adherence did not significantly differ between suppressed and non-suppressed children (p=0.25) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B419). Average adherence to lamivudine (97%) and stavudine (96%) did not differ by regimen.

At 1204 visits with scheduled MR, there were 381 visits (32%) where one or more medication was not returned. 174 (65%) children had at least one visit where medication was not returned; the proportion of children with missing MR did not differ by regimen. There was no association between suppression and not returning medications; 128 (65%) of suppressed and 46 (64%) of non-suppressed children ever had a visit with missing MR.

The relationships between viral suppression and adherence measured by MR at different thresholds (60–99%) for each drug individually and for the regimen as a whole are shown in Table 2. For children on the LPV/r-based regimen, MR adherence to each of the three drugs in the regimen (LPV/r, lamivudine or stavudine) individually and considered together predicted viral suppression (Table 2). For example, children receiving the LPV/r-based regimen who were at least 85% adherent to all drugs in the regimen, had 2.30-fold increase in the odds of viral suppression compared to children who were less adherent (Odds Ratio [OR] 2.30, 95% CI: 1.30–4.07). While it was a strong independent predictor of virologic suppression, adjustment for missed study visits did not change the relationship between MR adherence and virologic suppression. Addition of pre-treatment viral load (≥750,000 copies/mL) to the model tended to strengthen the relationship between adherence and viral suppression. Restriction of the analysis to children never treated with ritonavir strengthened the association between MR adherence and virologic suppression. In contrast, for children receiving the ritonavir-based regimen, the association between viral suppression and adherence to the regimen and to the individual drugs was weaker and inconsistent. Only adherence >85% with ritonavir specifically was significantly associated with viral suppression. This remained significant after adjusting for pre-treatment viral load and history of TB treatment (OR 2.08, 95% CI: 1.04–4.15).

Concordance of measures

There was poor consistency between reported adherence and MR. For those treated with LPV/r, at 184 visits where MR was <99% to any drug, only 19 (10%) caregivers reported a missed dose. Similarly, for those treated with ritonavir, at 171 visits with <99% adherence to any drug, only 19 (11%) caregivers reported a missed does. The kappa statistic between MR<99% to any drug and reported missed dose for LPV/r regimen visits was 0.04 suggesting agreement no better than chance (95% CI: −0.02–0.11) (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B420). At 361 visits with <99% adherence to any drug, there were 127 (35%) reports of a barrier to adherence. The most commonly report barrier for children treated with LPV/rat visits with <99% MR (n=185) adherence was that the child was uncooperative (10%). For children treated with ritonavir, the most commonly reported barriers at 171 visits with MR<99% were caregiver forgetting and fear of side effects, each reported at 21 visits (12%).

Predictors of medication adherence

Clinical, caregiver and socio-demographic characteristics at enrollment, were examined as independent predictors of non-adherence, using any MR of <85% for LPV/r and ritonavir regimens (Table 3). For children on LPV/r regimens, better socio-economic conditions, namely availability of electricity, television and refrigerator in the home, as well as having a mother who had completed secondary education, were found to be associated with better adherence.

DISCUSSION

High proportions of viral suppression and medication adherence were found in this cohort of infants and young children initiating protease inhibitor based antiretroviral treatment in South Africa. Overall, 197 of 269 (73%) children achieved viral suppression in the first 24 weeks of treatment and average child adherence to each of the antiretroviral medications measured was greater than 90%. Overall, 70% of children achieved ≥80% adherence at all visits to each of their medications, and more than half of children had ≥90% adherence. The finding of high levels of medication adherence in this cohort is in keeping with than previous studies.[12,24]

In this analysis, adherence as measured by caregiver report of missed doses was high and did not predict viral suppression. Endorsement of barriers to adherence was fairly common but was unrelated to virologic response. There was little or no internal consistency between report of missed doses and adherence ascertained by medication return. This is in keeping with previous findings on reported adherence and medication return which have also found that caregivers over-report adherence.[11,24,25] In contrast to one study from Zambia[12] which found MEMs caps to be the only adherence measure associated with viral suppression, we found strong associations with pharmacist-determined medication return, suggesting that carefully-conducted medication return is a valid method to ascertain adherence. We also found in this analysis that coming to all study visits during the 24 week follow-up period strongly predicted virologic suppression.

As measured by pharmacy medication return, any adherence <99% to a medication in the LPV/r-based regimen was associated with increased odds of not achieving viral suppression. Adherence with LPV/r itself was the most sensitive indicator showing significant associations with suppression over almost the full range of adherence thresholds. Considering the regimen as a whole, the association between adherence and viral suppression reached significance at the >85% cutoff. These findings suggest that adherence of >85% is an important cutoff for predicting virological suppression. They also suggest that

any non-adherence, particularly with the LPV/r dose itself, may jeopardize virologic outcomes. A small study from South Africa also found that virological suppression could be achieved with < 100% adherence for children on a LPV/r-based regimen (measured by electronic caps).[14] Our study did not compare PI-based regimens and regimens containing other drug classes such as non-nucleoside reverse transcriptase inhibitors and thus we cannot conclude whether PI-based regimens are more forgiving of poor adherence with regard to viral suppression.

In contrast to the findings for LPV/r-based regimens, children treated with ritonavir showed a weaker and less consistent relationship between adherence (as measured by medication return) and suppression. The lack of a clear relationship between medication adherence and virological suppression for children on ritonavir-based regimen is of limited relevance given that ritonavir is no longer advised for infants or for children being treated for TB while on ART.[26] Adherence to ritonavir as measured by pharmacy return was the lowest of all the drugs (although still high at 95% overall) and while we initially hypothesized that worse adherence with this regimen might explain its poor virological outcomes, this did not appear to be the case.[21] As per South African treatment guidelines at the time, children under six months of age were initiated on ritonavir-based ART and younger age has been associated with longer time to virological suppression.[27,28] This may in part help to explain the lack of association between adherence and viral suppression in children on ritonavir-based regimens.[29] Other than young age, co-treatment for TB was the predominant reason children were treated with the ritonavir-based regimen (in our cohort roughly half the children on ritonavir were under six months of age at ART initiation). It is not unlikely that the lack of relationship between adherence and viral suppression for children treated with ritonavir could also be driven by drug-drug interactions between the antiretroviral and anti-tuberculosis drugs. Data from South Africa have shown that rifampicin can significantly diminish lopinavir concentrations in young children.[30]

With regard to predicting adherence, better socio-economic status and mother's education level were associated with greater adherence with the LPV/r-based regimen which is in keeping with some prior studies.[11,12] A systematic analysis of pediatric adherence in several studies identified family poverty, low parental education and rural setting as predictors of non-adherence.[25] However, other results from South Africa found that neither household income, nor educational attainment of caregivers, were associated with adherence.[31] The association between socio-demographic factors and adherence requires further investigation.

Our analysis is unique in describing the relationship between adherence and viral suppression for each individual drug in two pediatric PI-based regimens. Previous studies have examined average combined adherence to all drugs in a pediatric regimen,[12] adherence to fixed-dose combination regimens [11,32] or have examined only one drug from a regimen.[14]

The limitations of this study include a short follow-up period of up to 24 weeks post ART initiation, representing only the initial phase of treatment. While this analysis was focused on early treatment outcomes, adherence has been shown to changeover time in both adults and children.[12,33] The dynamics of adherence with regard to viral suppression have been shown to vary with duration of treatment in adults.[9] There may be limitations with regard to extending these findings to longer durations of treatment. For instance, we did not find any association between the number of missing medication returns and virologic suppression, which has also been shown elsewhere.[12] However it is possible that during longer term follow-up, missing return of medication and/or repeated missed medication returns could impact virologic suppression. Another limitation is that children were followed at a single site in an urban setting in Johannesburg, South Africa which may limit the generalizability to more resource-limited settings. This cohort was also part of a clinical trial and received

enhanced adherence monitoring and support, which may have increased adherence to higher levels than would be expected in routine care.

What could not be controlled in the analysis were missing medication returns and medication returns of less volume of drug than expected. There did not appear to be any differences in missing medication returns for suppressed versus non-suppressed children however these circumstances represent gaps in adherence information. Further, we classified medication returns with less than the expected amount of drug as 100% adherent. This is in keeping with other analyses,[11] however it is not clear whether these medication returns indicate caregivers who re-gave the medication in the event of child spitting or vomiting, medication spillage or discarding of drug prior to the visit in order to appear to be adherent.

This study found that good adherence is achievable in young children initiating protease inhibitor-based ART in sub-Saharan Africa. Our data showed that caregiver reports of missed doses are a poor predictor of virologic response to treatment but systematic medication reconciliation correlated strongly with virologic response for children treated with a LPV/r-based regimen. While pharmacy reconciliation for pediatric formulations is more challenging than pill counts for adults, requiring the weighing of syrup bottles as well as staff training and time to complete reconciliations correctly, it can be an effective and valid method for measuring adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Frequency of reported adherence barriers and missed and incorrect doses among 269 children by regimen

	Number (%)subjects ever reported	Number (%)at each visit with report (both regimens)	Number (%) at each visit with report	
			LPV/r regimen	Ritonavir regimen
Adherence barriers	N=269	N=1351	N=697	N=507
Child uncooperative	108 (40%)	143 (12%)	72 (11%)	68 (14%)
Child refused to consume medication	69 (26%)	85 (7%)	46 (7%)	39 (8%)
Child spit up medication	61 (23%)	87 (7%)	45 (7%)	42 (8%)
Caregiver forgot to give medication	101 (38%)	125 (10%)	68 (10%)	56 (11%)
Afraid to give because of side effects	89 (33%)	121 (10%)	68 (10%)	52 (10%)
Did not want others to notice	39 (15%)	43 (4%)	26 (4%)	17 (3%)
1 or more of above barriers reported	203 (76%)	419 (35%)	**219 (33%)**	**196 (39%)** *
Reported missed doses				
Reported missed dose	75 (28%)	94 (8%)	**61 (9%)**	**30 (6%)** *
Incorrect dose given	8 (3%)	8 (1%)	6 (1%)	2 (1%)

* $p<0.05$

Table 2

Associations between viral suppression (<400 copies/mL by 24 weeks) and adherence defined by medication return (MR) at different thresholds (60–99%) for each drug individually and for the regimen as whole stratified by regimen

LPV/r-based regimen												
	LPV/r			**Lamivudine**			**Stavudine**			**Largest MR***		
Adherence level	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
60%	**3.18**	**1.10, 9.22**	**0.03**	2.73	0.86, 8.65	0.09	**3.04**	**1.05, 8.81**	**0.04**	**2.74**	**1.28–5.86**	**0.01**
70%	2.54	0.92, 7.06	0.07	2.85	0.98, 8.33	0.06	**2.49**	**1.04, 5.92**	**0.04**	**2.88**	**1.38–6.03**	**0.00**
80%	**3.25**	**1.49, 7.06**	**0.00**	**3.00**	**1.28, 7.04**	**0.01**	1.74	0.80, 3.79	0.16	**2.23**	**1.13–4.39**	**0.02**
85%	**2.24**	**1.06, 4.74**	**0.03**	**2.94**	**1.41, 6.13**	**0.00**	1.91	0.98, 3.70	0.06	**2.30**	**1.30–4.07**	**0.00**
90%	1.96	0.93, 4.14	0.08	**2.17**	**1.06, 4.46**	**0.04**	1.79	0.96, 3.36	0.07	1.71	0.95–3.08	0.07
95%	**2.19**	**1.13, 4.26**	**0.02**	1.75	0.87, 3.51	0.12	1.51	0.82, 2.76	0.18	1.65	0.95–2.85	0.07
99%	**2.22**	**1.23, 4.00**	**0.01**	1.72	0.87, 3.38	0.12	1.26	0.76, 2.09	0.38	1.52	0.93–2.50	0.10

Ritonavir-based regimen												
	Ritonavir			**Lamivudine**			**Stavudine**			**Largest MR**		
Adherence level	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
60%	1.24	0.27, 5.61	0.78	0.44	0.09, 2.19	0.31	0.50	0.10–2.41	0.39	0.71	0.23–2.17	0.54
70%	1.09	0.37, 3.26	0.87	0.29	0.06, 1.36	0.12	1.10	0.29, 3.51	0.98	0.79	0.34–1.81	0.58
80%	1.51	0.66, 3.45	0.32	0.49	0.17, 1.43	0.19	1.79	0.77, 4.14	0.17	1.46	0.77–2.75	0.25
85%	**2.00**	**1.03, 3.85**	**0.04**	0.70	0.27, 1.78	0.45	1.40	0.67, 2.95	0.37	1.41	0.80–2.48	0.24
90%	1.78	0.97, 3.30	0.06	0.75	0.33, 1.75	0.51	1.73	0.90, 3.31	0.10	1.41	0.83–2.39	0.20
95%	1.28	0.72, 2.27	0.40	0.82	0.39, 1.70	0.59	1.36	0.78, 2.36	0.28	1.10	0.67–1.81	0.72
99%	1.26	0.75, 2.10	0.38	0.90	0.46, 1.74	0.75	1.24	0.77, 1.99	0.37	1.20	0.77–1.87	0.42

*Largest MR = For each visit with at least one MR, the most non-adherent MR was used to classify adherence level for the visit

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Table 3

Predicators of non-adherence (MR adherence <85% to any drug) by regimen[†]

	Number (%)subjects	LPV/r Regimens			Ritonavir Regimens		
		MR <85% (N=636)			MR <85% (N=470)		
	N = 269	OR	CI	p-value	OR	CI	p-value
Age <12 months at enrollment	175 (65%)	1.01	0.61–1.67	0.96	0.85	0.47–1.53	0.59
Sex (female)	128 (48%)	1.23	0.74–2.04	0.42	0.98	0.55–1.73	0.94
Treatment naïve at enrollment	210 (78%)	0.97	0.53–1.77	0.92	1.11	0.51–2.39	0.79
Pre-treatment CD4 percentage <10%	41 (16%)	1.11	0.51–2.41	0.80	0.99	0.51–1.95	0.99
Pre-treatment Viral load >100,000	210 (89%)	0.81	0.47–1.39	0.45	1.24	0.66–2.33	0.50
Pre-treatment WHO stage 3 or 4	208 (77%)	1.36	0.73–2.55	0.34	1.59	0.74–3.46	0.24
Mother disclosed HIV status	233 (88%)	0.78	0.34–1.77	0.55	0.58	0.29–1.19	0.14
Mother on ART at enrollment	35 (13%)	0.65	0.32–1.32	0.23	0.30	.07–1.33	0.11
Mother (PCG) paid job	70 (26%)	1.19	0.67–2.11	0.56	1.77	0.98–3.21	0.06
Mother completed secondary education	95 (35%)	0.48	0.27–0.88	.02	1.08	0.61–1.89	0.80
Adults in home who don't know child's status	97 (36%)	0.89	0.53–1.49	0.66	1.19	0.67–2.12	0.55
Someone other than mother mainly cares for child	24 (13%)	1.16	0.55–2.46	0.70	1.44	0.70–2.99	0.33
Tap in home	117 (44%)	0.82	0.49–1.36	0.44	1.21	0.58–1.81	0.92
Electricity	224 (84%)	**0.38**	**0.22–0.66**	**0.00**	0.86	0.39–1.91	0.71
TV in home	208 (78%)	**0.47**	**0.27–0.81**	**0.01**	0.99	0.44–2.20	0.97
Fridge in home	168 (63%)	**0.44**	**0.27–0.73**	**0.00**	0.89	0.49–1.61	0.69
	Number (%)visits						
Someone other than mother gives medication	366/1200 (31%)	1.23	0.73–2.08	0.43	1.11	0.62–2.00	0.73

[†]Univariable logistic GEE model used to account for repeat measurements per child