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Adherence to antiretroviral therapy in a clinical cohort of HIV-infected children in East Africa

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Abstract

Objective

To describe antiretroviral therapy (ART) adherence and associated factors for a large HIV-infected pediatric cohort followed by sites of the East Africa International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium.

Methods

This study utilized prospectively collected clinical data from HIV-infected children less than 13 years of age who initiated ART within 4 clinical care programs (with 26 clinical sites) in Kenya, Uganda, and Tanzania and were followed for up to 6 years. Programs used one of 3 adherence measures, including 7-day quantitative recall, 7-day categorical recall, and clinician pill assessments. We fit a hierarchical, three-level, logistic-regression model to examine adherence, with observations nested within patient, and patients within the 26 sites providing pediatric HIV data to this analysis.

Results

In East Africa, 3,304 children, 52.0% male, were enrolled in care and were subsequently observed for a median of 92 weeks (inter-quartile range [IQR] 50.3–145.0 weeks). Median age at ART initiation was 5.5 years ([IQR] 3.0–8.5 years). “Good” adherence, as reported by each clinic’s measures, was extremely high, remaining on average above 90% throughout all years of follow-up. Longer time on ART was associated with higher adherence (adjusted Odds Ratio–aOR–per log-transformed week on ART: 1.095, 95% Confidence Interval–CI–[1.052–1.150].) Patients enrolled in higher-volume programs exhibited higher rates of clinician-assessed adherence (aOR per log-500 patients: 1.174, 95% CI [1.108–1.245]).
Significant site-level variability in reported adherence was observed (0.28), with even higher variability among patients (0.71). In a sub-analysis, being an orphan at the start of ART was strongly associated with lower ART adherence rates (aOR: 0.919, 95% CI [0.864–0.976]).

**Conclusions**

Self-reported adherence remained high over a median of 1.8 years in HIV care, but varied according to patient-level and site-level factors. Consistent adherence monitoring with validated measures and attention to vulnerable groups is recommended.

**Introduction**

The advent of antiretroviral therapy (ART) has transformed HIV infection from a rapidly terminal illness into a chronic disease. ART suppresses HIV replication, reduces HIV morbidity and mortality, and improves the lives of HIV-infected children [1–5] but successful long-term treatment depends on adherence to ART regimens. Patients who do not maintain adequate adherence to ART are at greater risk of viral resistance to the available antiretroviral drugs,[6–10] of immunologic decline resulting in opportunistic infections[11] and HIV disease progression,[12–17] and of transmitting resistant HIV at sexual debut.[18] Good ART adherence, typically defined as 90% or greater of doses taken as prescribed, decreases children’s HIV-related morbidity and mortality.[13, 19–21]

Over 90% of the world’s 3.4 million HIV-infected children live in the resource-limited settings of sub-Sahara Africa.[22, 23] While children’s access to ART in these settings is rapidly expanding, many patients still do not have access to second-line ART regimens and even fewer have access to third-line regimens.[24] Guidelines for pediatric HIV treatment recommend immediate ART initiation for HIV-infected infants, which should significantly reduce mortality among young children, but older children are expected to continue to have growing AIDS mortality.[25] Non-adherence and subsequent viral resistance could eliminate children’s limited treatment options.

Data from sub-Saharan Africa are still accumulating, but current estimates of pediatric ART adherence in resource-limited settings have ranged widely, with reports that 24.6% to 100% of their children have perfect adherence.[26–42] Despite this wide range, the majority of studies from resource-limited settings report good adherence among HIV-infected children; 76% of the studies included in a systematic review of pediatric ART adherence in low- and middle-income countries reported greater than 75% ART adherence, but few had been treating children for more than 3 years.[26] Most of these studies used caregiver reports of adherence, but self-reported adherence among older children or adolescents may yield reports of more non-adherence. In a study from Zimbabwe, 39% of adolescents reported suboptimal adherence, but significantly fewer reported suboptimal adherence if guardians were present in the room.[37] Other studies in sub-Saharan Africa have been able to prospectively measure adherence with more intensive and typically more valid methods, but these evaluations usually involve smaller numbers of children and collect adherence data prospectively for research. Such methods include home-based pill counts [35, 40], clinic-based pill counts [39], medication event monitoring systems (MEMS®) [36, 42, 43], plasma drug concentrations [38] and hair drug concentrations [41]. Few treatment programs in sub-Saharan Africa have been able to report on children’s adherence over the long-term or within large cohorts. In addition, these studies primarily focus on individual-level factors associated with adherence, without consideration of site- or facility-level contributions.
The objective of this study was to describe pediatric ART adherence for a large clinical cohort of HIV-infected children in East Africa. Data from the East Africa International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium were used to estimate ART adherence and to investigate both patient-level and site-level factors associated with ART non-adherence.

**Methods**

**Study design**

This study used prospectively collected, de-identified data from the computerized medical records of HIV-infected, pediatric patients treated in 26 sites belonging to 4 HIV care and treatment programs affiliated with the East Africa IeDEA consortium in Kenya, Uganda, and Tanzania until December 31, 2010. We sought to describe physician-assessed pediatric adherence, whether self-reported, proxy-reported, or assessed by the clinician via other methods, and associated patient or site-level factors. Each participating pediatric HIV clinic formally agreed to be included in the IeDEA collaboration, with local Institutional Review Board approvals.

**Study sites**

Established in 2006, IeDEA is a global data consortium funded by the United States National Institutes of Health to develop 7 regional data centers to compile global data to address research questions about HIV/AIDS treatment and care that cannot be answered with individual cohorts (see www.iedea.org). The East Africa IeDEA regional Consortium involves clinics providing HIV care and treatment in Kenya, Uganda, and Tanzania. Four of these clinical care programs provide care for children and adolescents (at 26 clinic sites) and are included in this analysis. These four programs are: 1) Academic Model Providing Access to Healthcare (AMPATH) clinical care system in western Kenya (AMPATH consists of 25 clinics and 40 satellite clinics; 17 of the main clinic sites provide pediatric care); 2) Family AIDS Care and Educational Services (FACES) in Kisumu, Kenya (FACES included 4 clinic sites, Family Health Options Kenya–FHOK, Lumumba, Pandpieri, and Tuungane); 3) the Mother-to-Child Transmission-Plus (MTCT-Plus) program (with 3 clinic sites, the Nyanza Provincial General Hospital in Kisumu, Kenya, the Makerere University–Johns Hopkins University Research Collaboration (MUJHU) in Kampala, Uganda and the St. Francis Hospital–Nsambya in Kampala, Uganda); and 4) the Tanzania Ministry of Health Community Development, Gender, Elderly and Children (MoHCDGEC) (with 2 clinic sites, Morogoro Regional Hospital in Morogoro, Tanzania; and the Tumbi Special Hospital in Kibaha, Tanzania). For the purpose of this analysis, AMPATH, FACES, MTCT-Plus, and MoHCDGEC are referred to as programs, where as the individuals clinics within each program are referred to as sites. In addition, any satellite clinic data from the AMPATH program were incorporated into their main “parent” clinic, which provides pediatric medical supervision.

Over the course of 10 years of collaboration in IeDEA, the programs have standardized protocols for data collection related to pediatric HIV care. However, the East Africa IeDEA sites each followed their own, local clinical protocols and procedures during the time period of the analysis and the systems may have implemented the protocols differently or to varying degrees. HIV-infected children were typically seen at least every three months. During the time period of this study, children’s CD4 counts were supposed to be measured once or twice a year for immunologic monitoring. Routine viral load monitoring was not performed at any of the sites at the time of these analyses. All sites had access to first-line antiretroviral therapy (ART) for children.
Ethical considerations

This analysis was approved as part of the projects of East African IeDEA by the Indiana University institutional research ethics board (IRB) as well as the local, and where appropriate, national regulatory bodies affiliated with the participating sites and regional data centers. As the analysis utilizes de-identified data collected within routine care, the local institutional research ethics boards or committees did not require written informed consent for patient-level data to be utilized in this analysis.

Study population

Eligible patients included HIV-infected children who had at least one medical visit at any of the pediatric HIV care sites of the East Africa IeDEA consortium between January 2002 and January 2009; had initiated ART; and had at least one ART adherence measure recorded in the electronic medical record database prior to 13 years of age. In most of these sites, children above 13 receive care within the adult clinics. Thus, the study population was limited to those still considered “children” at the time of the adherence assessment across the various care programs. Child anthropometric data were categorized according to the WHO Growth Standards [48] and orphanhood was defined using the standard definition of having a mother dead, a father dead, or both [49].

Data collection and adherence measures

A computerized clinical data collection system with a common set of variables for all sites was established for the participating IeDEA HIV care programs. Both site-level and patient-level data were extracted from the electronic medical record for this study and validated following established standard operating procedures within the East Africa IeDEA collaboration. The mechanisms for receiving and combining data from individual sites, including training on data collection; processing and cleaning; verifying data quality; and implementing methods for analyzing cohort data are all standardized.

The clinical sites recorded adherence data using one of 3 different adherence measures: a 7-day quantitative recall, a 7-day categorical recall of any missed pills, or a clinician pill assessment. Whether the recall items were asked of the child or the caregiver was not specified for the data within the electronic database. Clinical protocols at the sites using the recall methods generally direct the clinician to ask the child’s caregiver about adherence (proxy-report) unless the child is alone or the caregiver indicates that the child is primarily responsible for taking his/her own medicines, in which case the child should be asked directly (self-report). For the 7-day quantitative recall, adherence data were collected from responses to the question, “During the last 7 days, how many doses of his/her antiretroviral medicines did the patient take?” with potential response options of: “none,” “few,” “half,” “most,” and “all.” Good adherence was defined as reporting that “all” doses were taken. This adherence measure was used at the AMPATH and MTCT-plus sites. For the 7-day categorical recall of any missed pills, the caregiver or patient was asked “Has the patient missed any of his/her antiretroviral medicines did the patient take?” and the potential responses were only “yes” or “no”. This measure was used by the FACES sites, and good adherence was equivalent to a “no” response. Adherence was measured through a clinician pill assessment for the Tanzanian MoHCDGEC sites, where clinicians asked to see the medication remaining when a child presented for a return visit, did a visual check of the medication, and then recorded whether the amount of remaining medicine indicated good adherence (defined in their protocol as pills remaining suggesting two or fewer missed doses over the past month) or poor adherence (pills remaining suggesting three or more missed doses over the past month.) The clinician pill assessment did not quantify how
many pills are remaining, as would be usual for a standard “pill count.” These three different types of ART adherence measures were collapsed into a binary measure of “good” versus “poor” ART adherence per visit for all sites to create a summary outcome assessing the adherence across these sites.

**Statistical analyses**

We used descriptive statistics to describe this cohort of East African children at enrolment into care and at ART initiation. Adherence (“good” vs. “poor”) was described for various time periods after ART initiation, by site and by a number of factors including demographics, patient volume at the site (expressed as the number of patients within a site having recorded visits at each time point) and treatment course (expressed as weeks from ART initiation). Program attrition was defined as not having a visit for any reason for more than 90 days since database closure. The database did not distinguish between the end of observation due to mortality or treatment disengagement. Measures of time from ART initiation were censored at the time of attrition, and estimates of the probability of remaining on follow-up were produced using the Kaplan-Meier method. Conversely, times from ART start were censored at database closure or reaching one’s 13th birthday, and program attrition was considered the event of interest when estimates of program retention (defined as one-minus the probability of attrition) were calculated. The effect of adherence on program attrition was assessed via a Cox model with multiple adherence evaluations per patient considered as time-dependent covariates.

We fit a hierarchical, three-level logistic regression model, with observations nested within patients and patients within sites (sites were each of the 26 clinics belonging to the 4 East Africa IeDEA pediatric care programs participating in this study). We report the relative variability associated with the level “site” and the level “patient” to quantify the relative proportion of variability attributed to each factor. A few other patient-level and site-level factors were also used in the exploratory data analysis. With regard to patient-level factors we concentrated on age and gender as well as the duration of exposure to antiretroviral therapy. We also examined the effect of patient volume (number of patients per site at the same time point) as a proxy of program size, maturity but also burden on human and non-human resources. Statistical analyses were performed using R version 3.4.2 (2017-09-28) (the R Foundation for Statistical Computing).

**Results**

**Characteristics of pediatric HIV care in East Africa**

The East Africa IeDEA cohort included 3,304 HIV-infected children who had been started on ART at the care systems in Kenya, Uganda, and Tanzania (Table 1). Of the total cohort, the majority (79.1%) were followed at AMPATH sites in western Kenya. The median age at initiation of ART was 5.5 years (inter-quartile range [IQR] 3.0–8.5 years; Table 1). Just over half of the children (52.0%) were male. Data on orphan status were only collected for children followed at the AMPATH sites. Of the 1,962 children with orphan status known, 55.5% had at least one parent dead at initiation of ART. At their last visit, the children had been receiving ART for a median of 91.7 weeks (IQR 47.1–91.7 weeks). Program attrition (loss to follow-up or death) was 15.8% at one year post-ART initiation (95% CI: 14.5%-17.1%) and 24.3% (95% CI: 22.5%-26.0%) at two years. In a Cox analysis with good adherence considered as a time-dependent covariate (i.e., an analysis involving multiple observations per patient), the average (over all observations) impact of perfect adherence on the time until program attrition was to slightly reduce the hazard by almost 25% (hazard ratio 0.77, 95% CI 0.53–1.11). However, this reduction was not statistically significant (p-value 0.160).
Pediatric ART adherence in East Africa

The measures of adherence used by AMPATH, FACES, MTCT-Plus and the Tanzania MoHCDGEC programs, along with patient characteristics within each program, are listed in Table 2. Duration of observation after ART initiation varied greatly within program, with MTCT-Plus patients being observed the longest (median duration of observation 174 weeks, inter-quartile range–IQR– 112.1–230.9), while FACES patients were observed for the shortest duration (median 28.4 weeks, IQR 11.4–56.0 weeks).

Overall, the rates of pediatric adherence among the East Africa sites remained stable over time, at an average above 90% (range 93.6%-98.4%) throughout all years of follow-up, with a slight upward trend (Fig 1, black line). The average rates of “good” adherence by six-month period, after ART initiation, by site and overall are described in Fig 2. The sites in Tanzania, which used the clinician pill assessment for adherence measurement, had the highest reported levels of adherence. The overall trend was dominated by AMPATH (the largest care program).

In the hierarchical model, with observations nested within patients and patients within sites, the variance in reported adherence associated with the site (0.28) was about a third of the variance associated with individual patients (0.71). (Table 3). Longer time on ART was

| Table 1. Characteristics of East African HIV-infected children on antiretroviral therapy (N = 3,165). |
|-----------------------------------------------|
| Population Characteristics         | N (%) |
|-----------------------------------------------|
| Age at ART Initiation                 |       |
| < = 1 year                            | 171 (5.2%) |
| 1–3.0 years                          | 669 (20.2%) |
| 3.0–5.0 years                        | 666 (20.2%) |
| 5.0–7.0 years                        | 587 (17.8%) |
| 7.0–9.0 years                        | 507 (15.3%) |
| 9.0–11.0 years                       | 385 (11.7%) |
| 11.0–13.0 years                      | 290 (8.8%) |
| Median Age (years) at ART Initiation  | 5.5 (IQR 3.0–8.5 years) |
| Gender                               |       |
| Male                                  | 1717 (52.0%) |
| Female                                | 1587 (48.0%) |
| Orphan Status at ART Initiation (AMPATH only) | N = 1,962 |
| At Least 1 Parent Dead                | 1089 (55.5%) |
| Both Parents Alive                   | 873 (44.5%) |
| Tuberculosis at ART Initiation        |       |
| On Anti-TB Treatment                  | 578 (18.3%) |
| Not on Anti-TB Treatment              | 2587 (81.7%) |
| Median Weeks on ART (95% CI)          | 91.7 (IQR 88.0–95.1) |

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Pediatric ART adherence in East Africa

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Overall, the rates of pediatric adherence among the East Africa sites remained stable over time, at an average above 90% (range 93.6%-98.4%) throughout all years of follow-up, with a slight upward trend (Fig 1, black line). The average rates of “good” adherence by six-month period, after ART initiation, by site and overall are described in Fig 2. The sites in Tanzania, which used the clinician pill assessment for adherence measurement, had the highest reported levels of adherence. The overall trend was dominated by AMPATH (the largest care program).

In the hierarchical model, with observations nested within patients and patients within sites, the variance in reported adherence associated with the site (0.28) was about a third of the variance associated with individual patients (0.71). (Table 3). Longer time on ART was

| Table 2. Measures of adherence, patient characteristics and duration of follow-up by program in East Africa. |
|-----------------------------------------------|
| HIV Care & Treatment Program                  |
| AMPATH                                      |
| FACES                                       |
| MTCT-Plus                                   |
| TZ MoHCDGEC                                  |
| N                                           | 2613 | 190 | 268 | 233 |
| Adherence Measure Used At Site               | 7 day| 7 day, any missed | 7 day | 1 month pill count |
| Median Age at ART Initiation (IQR)           | 5.6 (3.2–8.5) | 5.2 (2.5–8.8) | 2.5 (0.9–5.9) | 7.1 (4.0–10.1) |
| Median weeks on ART (95% CI)                | 90.7 (48.0–126.1) | 28.4 (11.4–56.0) | 174 (112.1–230.9) | 92 (70–110) |
| Male children (%)                           | 1372 (52.5%) | 98 (51.6%) | 135 (50.4%) | 112 (48.1%) |

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associated with slightly higher adherence (aOR of the log-transformed week on ART 1.10, 95% Confidence Interval [1.005–1.015]; p-value < 0.001). (Table 3) There was no difference in adherence depending on the gender of the child or the age at the start of ART. Reported adherence was higher within the programs that saw a higher volume of pediatric patients (Table 3).

Sub-analysis by orphan status

Orphan status was collected only at the start of therapy and only at AMPATH. Consequently, analyses assessing the impact of orphan status on ART adherence were limited to sites within this program. Results of the multi-level logistic-regression model applied in this analysis (with observations nested within AMPATH clinic sites) are shown in Table 4. Orphan status is associated with significantly lower odds of good adherence (aOR: 0.78, 95% Confidence Interval [0.64–0.95]). The impact of the remaining factors considered was consistent as described above for the complete data analysis.

Discussion

The combined data from pediatric HIV care programs across East Africa suggest that the majority of HIV-infected children in these settings have good ART adherence on clinical assessments over a fairly long follow-up period (Fig 2). This level of adherence is similar to adherence reported over varying time periods within smaller cohorts of patients from East Africa [50–52] and elsewhere in sub-Saharan Africa. [29, 33] Our analyses of a larger cohort, with comparisons between sites and evaluation of adherence over time, indicates good ART adherence while suggesting some critical targets for measuring, supporting and improving adherence.
While ART adherence among East African children was high overall, certain groups may be prone to non-adherence. Better adherence among younger children suggests that adherence may become worse as children grow older, highlighting the potential challenges of maintaining good ART adherence during adolescence.[53] However, this study include predominately younger children, with only a weak suggestion of diminishing adherence with age. Following adherence closely as perinatally-infected pediatric cohorts age into adolescence is a key priority. These data did highlight that the sites with larger patient volumes had more reports of good pediatric adherence. This finding related to high-volume sites merits closer examination.

Table 3. Multivariate hierarchical model of the odds of good adherence with observations nested within patients and patients within clinical sites.

| Effect of . . .                  | OR      | 95% CI      | p-value |
|---------------------------------|---------|-------------|---------|
| Weeks on ART*                   | 1.100   | 1.052–1.150 | <0.001  |
| Gender: Male                    | 0.943   | 0.835–1.065 | 0.344   |
| Age at ART Start (per year)     | 0.986   | 0.968–1.004 | 0.118   |
| Volume of Patients (in 500-Patient Increments)* | 0.852   | 0.803–0.903 | <0.001  |

* Log-transformed
It may be that these sites coping with large patient volumes do not actually have better adherence, but are, in fact, not detecting poor adherence. A site with over-burdened clinicians and support staff may not have the time or resources to thoroughly assess adherence with individual families. On the other hand, high-volume sites may be more experienced in detecting and managing families’ struggles with pediatric adherence, resulting in true improvements in adherence. The larger, referral centers also often provide care for a sicker population of children, creating a form of referral bias, and it is possible that they pay closer attention to adherence for these sicker children at risk of treatment failure. These data do not allow conclusions to be drawn on this issue.

These analyses provide a unique opportunity to assess the variability in adherence that could be attributed to site-level differences, in comparison with the individual patient-level factors typically evaluated. The variance in reported adherence associated with the site was almost one third as high as the variance associated with the individual patients, even after all site-level factors were accounted for. This observation points that there are significant program-level factors not accounted for in these data, but also underscore the fact that, in addition to varying patient characteristics, program-level characteristics are critical in maintaining or improving adherence. The odds of good adherence increased exponentially with increasing volume of patients, for example. Addressing pediatric adherence not just within the context of a given child and caregiver, but as a pervasive clinical program issue appears to be a key strategy for maintaining our gains in the treatment of HIV-infected children over the long-term.

These analyses reveal some important issues related to adherence measurement. The sites that used pill counts reported much higher estimates of adherence, suggesting that the pill counts may not have accurately captured instances of non-adherence as higher adherence estimates are typically considered less accurate. These findings may seem surprising since, in many reports, pill counts have been considered more accurate than recall measures. However, the pill counts described across the East Africa clinical sites in this analysis were unlike the pill counts used in research settings. In this study, using data from routine clinical care, the actual number of pills dispensed at each visit and any pills remaining at the next visit were not recorded. Thus, even though the adherence measurement was called a “pill count”, there were at best only visual checks of the number of pills remaining, which in turn may have reduced the validity of these measures. Moreover, the sites did not use a specific method for weighing or estimating the volume of liquid medications, which can alter the accuracy of a “pill count” for all of the pediatric patients on liquid formulations. Pill counts were not directly compared with self-reports or proxy-reports in the sites taking part in this study, so no comparison can be made as to the pill count validity compared to other measures. Furthermore, the settings using recall measures did not employ any other comparative measures of adherence, such as pill counts or electronic dose monitoring. Although proxy-reports or self-reports are the most widely used method of adherence assessment, these reports also tend...
to overestimate adherence [35, 37, 38, 40, 42, 43, 54]. No attempt was made to compare the levels of adherence as measured by the three methods because no patient was evaluated with more than one method. Thus, the method and the site effects were confounded (i.e., any differences in the levels of adherence could not be reasonably disentangled from the effect that the sites had on adherence). Reliable, validated measures of ART adherence for children are urgently needed. The impact of orphanhood on adherence could only be assessed within the AMPATH program in Kenya, as this was the only program collecting data on the orphan status of children. The sub-analyses of this large sub-population of children suggested that orphanhood is another factor that may be associated with reduced adherence levels. Given the critical role of the caregiver in administering medicines to children and in supervising medication-taking as children age, in combination with the potential economic and social upheaval that come with the death of a child’s parent or parents, this is not a surprising finding. The potential impact of orphanhood on children’s adherence points to the need to find strategies to support this vulnerable population, as well as to ensure measurement of orphan status for children across sub-Saharan Africa. A final limitation concerns trend toward increasing rates of good adherence over time. It is possible that, since adherence measures are taken only from patients returning to clinic, overall adherence may be overestimated as we begin to sample from the smaller group of patients that is retained in care over time. In the Cox analysis we performed to assess the possible relationship of imperfect adherence with the hazard of program attrition, however, we did not observe a strong association between lower adherence and higher hazard of loss to program or mortality.

In addition to limitations with respect to measuring adherence, this study has several further limitations that require consideration. We did not evaluate the relationship of clinical outcomes such as World Health Organization (WHO) or Centers of Disease Control (CDC) staging, CD4 counts or percentages to the self-report or proxy-reports of adherence. The clinical outcomes for children cared for within these sites were difficult to assess with accuracy from the available data. Viral load measurements were not available at these sites during the time of this study. While CD4 counts and clinical staging should have been collected or performed for most of the enrolled children, there were a paucity of data for these outcomes from many of the sites. Because of the gaps in the CD4 results in the clinical data, we chose to report adherence alone across the broad range of children, rather than to restrict the analyses to only those with complete CD4 data which would have severely limited our study population (and potentially have biased our results). The limitation of lacking CD4 comparisons is somewhat allayed by findings in other studies where reported adherence was not consistently associated with CD4 counts [26, 57]. The clinical staging data, while contained in these clinical data, are less useful for comparisons with adherence because patients always remain at the highest level of clinical staging that they have reached regardless of response to therapy. Good adherence, even if it results in an improved clinical picture, would thus fail to move a patient to a lower or less severe clinical stage.

Our data were limited to those variables available within the common dataset across the East Africa IeDEA sites. Viral loads were not available, nor were some other variables of potential importance, such as caregivers’ HIV status, orphan status for all children, and over time, or orphan care setting. Our study may also have underestimated the extent of ART non-adherence because adherence was based on in-clinic assessments and thus potentially compounded by clinic non-adherence or social desirability biases. While patients may have some extra medication supplies and should report non-adherence from missed visits during their subsequent visits, clinic-based ART assessments likely underestimate ART non-adherence. In addition, the nature of the observational cohort precludes us from making causal inferences.

Despite these limitations, this study has critical advantages that add to the current literature on pediatric ART adherence. The study involves a large cohort from an entire world region,
across multiple programs, caring for children and following them for a number of years. The children in the analysis span a large spectrum of ages, and their general characteristics suggest that they are representative of a typical population of HIV-infected children in East Africa if not throughout sub-Saharan Africa. The representativeness of our population is also buoyed by the fact that we have captured data from both large and small care systems, while maintaining this wide regional representation. Consequently, these data allow for both care systems and policy makers to consider the challenges to pediatric ART adherence as we attempt to maintain the survival of an entire generation, from infancy and into adulthood living with HIV.

Conclusions

Effective disease management for children with HIV depends on sustaining high rates of adherence. Although ART adherence appears to be very good among children in East Africa, HIV care systems in resource-limited settings must continue to measure, sustain, and improve ART adherence. Reliable, valid, affordable measurement strategies that can be employed for routine adherence measurement are urgently needed.

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Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the view of the Indiana University School of Medicine, Moi University, or the IeDEA consortium. The authors have no conflicts of interest to disclose.

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References

1. Doerholt K, Duong T, Tookey P, Butler K, Lyall H, Sharland M, et al. Outcomes for human immunodeficiency virus-1-infected infants in the United Kingdom and Republic of Ireland in the era of effective antiretroviral therapy. Pediatr Infect Dis J 2006, 25:420–426. https://doi.org/10.1097/01.inf.0000214994.44346.d3 PMID: 16645506

2. Gibb DM, Duong T, Tookey PA, Sharland M, Tudor-Williams G, Novelli V, et al. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. Br J 2003, 327:1019. https://doi.org/10.1136/bmj.327.7422.1019 PMID: 14593035

3. Gibb DM, Goodall RL, Giacomelli V, McGee L, Compagnucci A, Lyall H. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. Pediatr Infect Dis J 2003, 22:56–62. https://doi.org/10.1097/01.inf.000047674.63657.cd PMID: 12544410

4. Nyandiko WM, Ayaya S, Nabakwe E, Tenge C, Sidle JE, Yiannoutsos CT, et al. Outcomes of HIV-infected orphaned and non-orphaned children on antiretroviral therapy in western Kenya. J Acquir Immune Defic Syndr 2006, 43:418–425. https://doi.org/10.1097/01.qai.0000243122.52282.89 PMID: 17099313

5. Progress on global access to HIV antiretroviral therapy: a report on “3 by 5” and beyond. In: World Health Organization; 2006.

6. Mullen J, Leech S, O’Shea S, Chrystie IL, Du Mont G, Ball C, et al. Antiretroviral drug resistance among HIV-1 infected children failing treatment. J Med Virol 2002, 68:299–304. https://doi.org/10.1002/jmv.10203 PMID: 12226814

7. Tam LW, Chui CK, Brumme CJ, Bangsberg DR, Montaner JS, Hogg RS, et al. The Relationship Between Resistance and Adherence in Drug-Naive Individuals Initiating HAART Is Specific to Individual Drug Classes. J Acquir Immune Defic Syndr 2008.

8. Bangsberg DR, Hecht FM, Charlebois ED, Zolopa AR, Holodniy M, Sheiner L, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. Aids 2000, 14:357–366. PMID: 10770537

9. Bangsberg DR, Kroetz DL, Deeks SG. Adherence-resistance relationships to combination HIV antiretroviral therapy. Curr HIV/AIDS Rep 2007, 4:65–72. PMID: 17547827

10. Gavin PJ, Yoge R. The role of protease inhibitor therapy in children with HIV infection. Paediatr Drugs 2002, 4:561–607. PMID: 12175273

11. San-Andres FJ, Rubio R, Castilla J, Pulido F, Palao G, de Pedro I, et al. Incidence of acquired immunodeficiency syndrome-associated opportunistic diseases and the effect of treatment on a cohort of 1115 patients infected with human immunodeficiency virus, 1989–1997. Clin Infect Dis 2003, 36:1177–1185. https://doi.org/10.1086/374358 PMID: 12715314

12. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. Aids 2001, 15:1181–1183. PMID: 11418722

13. Van Dyke RB, Lee S, Johnson GM, Wiznia A, Mohan K, Stanley K, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. Pediatrics 2002, 109:e61. PMID: 11927734

14. Gross R, Yip B, Lo Re V 3rd, Wood E, Alexander CS, Harrigan PR, et al. A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. J Infect Dis 2006, 194:1108–1114. https://doi.org/10.1086/507680 PMID: 16991085
15. Lima VD, Harrigan R, Bangsberg DR, Hog RS, Gross R, Yip B, et al. The Combined Effect of Modern Highly Active Antiretroviral Therapy Regimens and Adherence on Mortality Over Time. *J Acquir Immune Defic Syndr* 2009, 50:529–536. https://doi.org/10.1097/QAI.0b013e31819675e9 PMID: 19223785

16. Hog RS, Heath K, Bangsberg D, Yip B, Press N, O’Shaughnessy MV, et al. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. *AIDS* 2002, 16:1051–1058. PMID: 11953472

17. Garcia de Olalla P, Knobel H, Carmona A, Guelar A, Lopez-Colomes JL, Cayla JA. Impact of adherence and highly active antiretroviral therapy on survival in HIV-infected patients. *J Acquir Immune Defic Syndr* 2002, 30:105–110. PMID: 12048370

18. Remien RH, Exner TM, Morin SF, Ehrhardt AA, Johnson MO, Correale J, et al. Medication adherence and sexual risk behavior among HIV-infected adults: implications for transmission of resistant virus. *AIDS Behav* 2007, 11:663–675. https://doi.org/10.1007/s10461-006-9201-8 PMID: 17243012

19. Little K, Thorne C, Luo C, Bunders M, Ngongo N, McDermott P, et al. Disease progression in children with vertically-acquired HIV infection in sub-Saharan Africa: reviewing the need for HIV treatment. *Curr HIV Res* 2007, 5:139–153. PMID: 17346131

20. Kabue MM, Kekitiinwa A, Maganda A, Rissors JM, Chan W, Kline MW. Growth in HIV-infected children receiving antiretroviral therapy at a pediatric infectious diseases clinic in Uganda. *AIDS Patient Care STDS* 2008, 22:245–251. https://doi.org/10.1089/apc.2007.0049 PMID: 18298315

21. Walker AS, Ford D, Mulenga V, Thomason MJ, Nunn A, Chintu C, et al. Adherence to Both Cotrimoxazole and Placebo is Associated with Improved Survival Among HIV-Infected Zambian Children. *AIDS Behav* 2008.

22. The State of the World’s Children 2009. In: United Nations Children’s Fund; 2009.

23. UNAIDS. UNAIDS Report on the Global AIDS Epidemic 2010. In. Edited by UNAIDS. Geneva, Switzerland: UNAIDS; 2010.

24. Boyd MA, Cooper DA. Second-line combination antiretroviral therapy in resource-limited settings: facing the challenges through clinical research. *AIDS* 2007, 21 Suppl 4:S55–63.

25. Johnson LF, Davies MA, Moultrie H, Sherman GG, Bland RM, Rehle TM, et al. The effect of early initiation of antiretroviral treatment in infants on pediatric AIDS mortality in South Africa: a model-based analysis. *Pediatr Infect Dis J* 2012, 31:474–480. https://doi.org/10.1097/INF.0b013e3182456ba2 PMID: 22189531

26. Vreeman RC, Wiehe SE, Pearce EC, Nyandiko WM. A systematic review of pediatric adherence to antiretroviral therapy in low- and middle-income countries. *Pediatr Infect Dis J* 2008, 27:686–691. https://doi.org/10.1097/INF.0b013e31816dd325 PMID: 18574439

27. Bhattacharya M, Dubey AP. Adherence to antiretroviral therapy and its correlates among HIV-infected children at an HIV clinic in New Delhi. *Annals of tropical paediatrics* 2011, 31:331–337. https://doi.org/10.1179/1465328111Y.0000000031 PMID: 22041467

28. Yoder RB, Nyandiko WM, Vreeman RC, Ayaya SO, Gisore PO, Braithstein P, et al. Long-term impact of the Kenya post-election crisis on clinic attendance and medication adherence for HIV-infected children in western Kenya. *Journal of acquired immune deficiency syndromes* 2011.

29. Haberer JE, Cook A, Walker AS, Ngambi M, Ferrier A, Mulenga V, et al. Excellent adherence to antiretrovirals in HIV+ Zambian children is compromised by disrupted routine, HIV nondisclosure, and paradoxical income effects. *PloS one* 2011, 6:e18505. https://doi.org/10.1371/journal.pone.0018505 PMID: 21533031

30. Nassali M, Nakajjako D, Kyabayinze D, Beyeza J, Okoth A, Mutyaba T. Access to HIV/AIDS care for mothers and children in sub-Saharan Africa: adherence to the postnatal PMTCT program. *AIDS Care* 2009, 21:1124–1131. https://doi.org/10.1080/09540120802707467 PMID: 20024771

31. Polisset J, Amonetou F, Arrive E, Aho A, Perez F. Correlates of adherence to antiretroviral therapy in HIV-infected children in Lome, Togo, West Africa. *AIDS and Behavior* 2009, 13:23–32. https://doi.org/10.1007/s10461-008-9437-6 PMID: 18654845

32. Mukhtar-Yola M, Adeleke S, Gwarzo D, Ladan ZF. Preliminary investigation of adherence to antiretroviral therapy among children in Aminu Kano Teaching Hospital, Nigeria. *AJAR* 2006, 5:141–144. https://doi.org/10.2989/16085900609490374 PMID: 25875238

33. Muller AD, Bode S, Myer L, Roux P, von Steinbuchel N. Electronic Measurement of Adherence to Pediatric Antiretroviral Therapy in South Africa. *Pediatr Infect Dis J* 2008.

34. Elise A, France AM, Louise WM, Bata D, Francois R, Roger S, et al. Assessment of adherence to highly active antiretroviral therapy in a cohort of African HIV-infected children in Abidjan, Cote d’Ivoire. *J Acquir Immune Defic Syndr* 2005, 40:498–500. PMID: 16280708
35. Biressaw S, Abegaz WE, Abebe M, Taye WA, Belay M. Adherence to Antiretroviral Therapy and associated factors among HIV infected children in Ethiopia: unannounced home-based pill count versus caregivers’ report. *BMC Pediatr* 2013, 13:132. https://doi.org/10.1186/1471-2431-13-132 PMID: 24229394

36. Eby J, Chapman J, Marukutira T, Anabwani G, Tshume O, Leposodi O, et al. The adherence-outcome relationship is not altered by diary-driven adjustments of microelectronic monitor data. *Pharmacoepidemiol Drug Saf* 2015, 24:1313–1320. https://doi.org/10.1002/pds.3887 PMID: 26564882

37. Gross R, Bandason T, Langhaug L, Mujuru H, Lowenthal E, Ferrand R. Factors associated with self-reported adherence among adolescents on antiretroviral therapy in Zimbabwe. *AIDS Care* 2015, 27:322–326. https://doi.org/10.1080/09540121.2014.969676 PMID: 25338010

38. Mghamba FW, Minzi OM, Massawe A, Sasi P. Adherence to antiretroviral therapy among HIV infected children measured by caretaker report, medication return, and drug level in Dar Es Salaam, Tanzania. *BMC Pediatr* 2013, 13:95. https://doi.org/10.1186/1471-2431-13-95 PMID: 23768248

39. Nabukeera-Barungi N, Elyanu P, Asire B, Katureebe C, Lukabwe I, Namusoko E, et al. Adherence to antiretroviral therapy and retention in care for adolescents living with HIV from 10 districts in Uganda. *BMC Infect Dis* 2015, 15:520. https://doi.org/10.1186/s12879-015-1265-5 PMID: 26573923

40. Nsheha AH, Dow DE, Kapanda GE, Hamel BC, Msuya LJ. Adherence to antiretroviral therapy among HIV-infected children receiving care at Kilimanjaro Christian Medical Centre (KCMC), Northern Tanzania: A cross-sectional analytical study. *Pan Afr Med J* 2014, 17:238. https://doi.org/10.11604/pamj.2014.17.238.2280 PMID: 25170382

41. Olds PK, Kiwanuka JP, Nansera D, Huang Y, Bacchetti P, Jin C, et al. Assessment of HIV antiretroviral therapy adherence by measuring drug concentrations in hair among children in rural Uganda. *AIDS Care* 2015, 27:327–332. https://doi.org/10.1080/09540121.2014.983452 PMID: 25483955

42. Vreeman RC, Nyandiko WM, Liu H, Tu W, Scanlon ML, Slaven JE, et al. Measuring adherence to antiretroviral therapy in children and adolescents in western Kenya. *J Int AIDS Soc* 2014, 17:19227. https://doi.org/10.7448/IAS.17.1.19227 PMID: 25427633

43. Vreeman RC, Nyandiko WM, Liu H, Tu W, Scanlon ML, Slaven JE, et al. Comprehensive evaluation of caregiver-reported antiretroviral therapy adherence for HIV-infected children. *AIDS Behav* 2015, 19:626–634. https://doi.org/10.1007/s10461-015-0998-x PMID: 25613594

44. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braithstein P, et al. Cohort Profile: The international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. *International journal of epidemiology* 2011.

45. Einterz RM, Kimaiyo S, Mengech HN, Khwa-Otsyula BO, Esamai F, Quigley F, et al. Responding to the HIV pandemic: the power of an academic medical partnership. *Acad Med* 2007, 82:812–818. https://doi.org/10.1097/0.01ACM.0b013e3180c29f1 PMID: 17762264

46. Kulzer JL, Penner JA, Merima R, Oyaro P, Oyanga AO, Shade SB, et al. Family model of HIV care and treatment: a retrospective study in Kenya. *Journal of the International AIDS Society* 2012, 15:8. https://doi.org/10.1186/1758-2652-15-8 PMID: 22353953

47. Myer L, Rabkin M, Abrams EJ, Rosenfield A, El-Sadr WM, Columbia University M-PI. Focus on women: linking HIV care and treatment with reproductive health services in the MTCT-Plus Initiative. *Reprod Health Matters* 2005, 13:136–146. PMID: 16035607

48. Group WMGRS. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. In: Geneva: World Health Organization; 2006.

49. UNICEF. Orphans. In: UNICEF; 2012.

50. Vreeman RC, Wiehe SE, Ayaya SO, Musick BS, Nyandiko WM. Association of antiretroviral and clinic adherence with orphan status among HIV-infected children in Western Kenya. *Journal of acquired immune deficiency syndromes* 2008, 49:163–170. https://doi.org/10.1097/QAI.0b013e318183a996 PMID: 18769353

51. Bikaako-Kajura W, Luyirika E, Purcell DW, Downing J, Kaharufu Z, Mermim J, et al. Disclosure of HIV status and adherence to daily drug regimens among HIV-infected children in Uganda. *AIDS Behav* 2006, 10:S85–93. https://doi.org/10.1007/s10461-006-9141-3 PMID: 16791525

52. Nabukeera-Barungi N, Kalyesuba I, Kekitiinwa A, Byakika-Tusiime J, Musoke P. Adherence to antiretroviral therapy in children attending Mulago Hospital, Kampala. *Ann Trop Paediatr* 2007, 27:123–131. https://doi.org/10.1179/146532807X192499 PMID: 17565809

53. Lowenthal ED, Bakeera-Kitaka S, Marukutira T, Chapman J, Goldrath K, Ferrand RA. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. *Lancet Infect Dis* 2014, 14:627–639. https://doi.org/10.1016/S1473-3099(13)70363-3 PMID: 24406145
54. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. *AIDS Behav* 2006, 10:227–245. https://doi.org/10.1007/s10461-006-9078-6 PMID: 16783535

55. Haberer JE, Kiwanuka J, Nansera D, Ragland K, Mellins C, Bangsberg DR. Multiple Measures Reveal Antiretroviral Adherence Successes and Challenges in HIV-Infected Ugandan Children. *PloS one* 2012, 7:e36737. https://doi.org/10.1371/journal.pone.0036737 PMID: 22590600

56. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. *Current HIV/AIDS reports* 2009, 6:194–200. PMID: 19849962

57. 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:e1371–1383. https://doi.org/10.1542/peds.2006-1232 PMID: 17533177