Association of Antiretroviral and Clinic Adherence With Orphan Status Among HIV-Infected Children in Western Kenya

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Background: Pediatric adherence to antiretroviral therapy (ART) is not well studied in resource-limited settings. Reported ART adherence may be influenced by contextual factors, such as orphan status.

Objectives: The objectives of this study were to describe self- and proxy-reported pediatric ART adherence in a resource-limited population and to investigate associated contextual factors.

Patients and Methods: This was a retrospective study involving pediatric, HIV-infected patients in Western Kenya. We included patients aged 0–14 years, who were on ART and had at least 1 adherence measurement (N = 1516). We performed logistic regression to assess the association between orphan status and odds of imperfect adherence, adjusting for sex, age, clinic site, number of adherence measures, and ART duration, stratified by age and ART duration.

Results: Of the 1516 children, only 33% had both parents living when they started ART. Twenty-one percent had only father dead, 28% had only mother dead, and 18% had both parents dead. Twenty-nine percent reported imperfect ART adherence. The odds of ART nonadherence increase for children with both parents dead. Fifty-seven percent of children had imperfect clinic adherence. There was no significant association between orphan status and imperfect clinic adherence.

Conclusions: The majority of pediatric patients in this resource-limited setting maintained perfect ART adherence, though only half kept all scheduled clinic appointments. Understanding contextual factors, such as orphan status, will strengthen adherence interventions.

Key Words: adherence, antiretroviral therapy, ART, HIV, AIDS, orphan, pediatrics

INTRODUCTION

Antiretroviral therapy (ART) effectively suppresses HIV replication, reduces mortality, and improves the lives of children and adults with HIV.[1–5] Without high levels of adherence, viral resistance to drugs[6] and opportunistic infections can develop.[7] With 2.1 million children under the age of 15 years currently living with HIV,[8] measuring and supporting long-term pediatric adherence to ART become a public health priority. For pediatric populations within developed countries, systematic reviews indicate that the majority of pediatric HIV care programs report suboptimal adherence[9–11]; 33 of the 55 studies in the most recent critical analysis estimated adherence rates at less than 75%.[9] Although 90% of HIV-infected children live in Africa,[8] assessments of pediatric adherence to ART in Africa have emerged only recently, with rates of ART adherence estimated between 60% and 80%.[12–18] Comprehensive assessment and estimates of pediatric adherence in resource-limited settings are urgently needed.[19]

Understanding the correlates and context of pediatric adherence also presents an important challenge for adherence measurement, prediction, and interventions. Pediatric adherence to daily drug regimens is embedded within a complex context that includes individual patients and their therapy, caregivers, households, and society.[11,20] Children with HIV in resource-limited settings likely receive their ART in a unique context, one that includes much higher rates of orphanhood, malnutrition, and coexisting infections such as tuberculosis.[8] Data to explain the correlates of pediatric adherence in resource-limited settings are just beginning to accumulate. Family and caregiver factors, including parental beliefs,[20,21] education and income level,[20,22] disclosure of the child's HIV status,[15,16] and disorganized family structures,[20,22] have been significantly associated with adherence. However, in other

studies, parents' social class[14] and available social support[16] were not significantly associated with adherence. Thus, further assessment of how family characteristics impact adherence is needed.

Among these contextual characteristics, orphan status merits particular attention. An estimated 14 million children are orphaned as a result of HIV, with 80% of these orphans living in sub-Saharan Africa.[23] Orphan status defines crucial elements of a child's social and economic context. Whereas several studies have reported adverse outcomes for orphans, including poorer health and nutrition,[24–26] higher hospitalization rates,[27] lower school attendance,[28,29] and higher childhood mortality,[30] other studies reveal variable associations between orphan status and health indicators.[25,27,30–32] In some studies from resource-limited settings, orphan status has been associated with ART nonadherence,[20, 22] whereas other studies have not found a significant correlation between nonadherence and orphan status.[13,16,33,34] The particular orphan care system may play a role; one study suggests that orphans with institutional caregivers have better adherence than those with noninstitutional caregivers.[22] The variable effects of orphan status on dimensions of HIV care and outcomes merit further examination.

HIV care systems in resource-limited settings are rapidly growing in capacity. As these care systems scale up, the opportunities to investigate factors associated with adherence to ART also expand. Our cohort of HIV-infected children within Western Kenya has grown from 1442 children in March, 2005, to over 9700 children in November, 2007.[13] Within this growing pediatric HIV care system in Kenya, we sought to describe self- or proxy-reported pediatric adherence to ART and associated factors, including whether orphan status was associated with the child's adherence to ART. In addition, we evaluated clinic adherence and its correlates.

PATIENTS AND METHODS

Study Design

This retrospective study used prospectively collected, de-identified data from the computerized medical records of HIV-infected, pediatric patients treated in the Academic Model for the Prevention and Treatment of HIV/AIDS (AMPATH) clinical care system in Western Kenya. The study was approved by the Institutional Research and Ethics Committee of the Moi University School of Medicine and Moi Teaching and Referral Hospital (Eldoret, Kenya) and the Institutional Review Board of the Indiana University School of Medicine (Indianapolis, IN).

Study Site

Since 1990, Indiana University School of Medicine has had a collaborative partnership with Moi University School of Medicine in Eldoret, Kenya.[35] AMPATH was created in 2001 as a joint initiative among these 2 medical schools and Moi Teaching and Referral Hospital to provide an HIV care system for patients in Western Kenya.[35–38] Over 63,000 pediatric and adult patients are treated within AMPATH, with 9720 children under the age of 14 years currently receiving care and over

2100 children currently on ART (as of November 29, 2007). A computerized medical record system supports clinical care and research,[39] and the outcomes of adult and pediatric patients have previously been reported.[13,40]

AMPATH operates an urban referral clinic at the Moi Teaching and Referral Hospital in Eldoret, Kenya, a national tertiary referral hospital serving a catchment area of approximately 13 million people. Comprehensive HIV care services for children are also provided at 16 outlying outpatient clinics (Mosoriot, Turbo, Burnt Forest, Amukura, Naitiri, Chulaimbo, Webuye, Teso, Kitale, Kapenguria, Mt Elgon, Iten, Karnet, Busia, Port Victoria, and Khuyangu), located within district hospitals and health centers throughout Western Kenya. HIV care is provided by physicians and clinical officers trained and mentored within AMPATH.[41]

Study Population

Eligible patients included any child seen in any of 17 AMPATH clinics between June 2003 and March 2007 who were less than 14 years, were HIV infected, had initiated ART, and had at least 1 adherence measurement recorded in the electronic medical record database. In the AMPATH clinic system, children 14 years and older receive care within the adult clinics. Thus, the study population was limited to children receiving care within the pediatric setting to examine a population receiving care from pediatric providers.

Clinical Procedures

Throughout the period of the study, clinicians followed detailed, locally developed protocols consistent with World Health Organization guidelines. HIV infection was documented by DNA polymerase chain reaction (Amplicor, Roche, Basel, Switzerland) for children younger than 18 months and by 2 parallel HIV rapid enzyme-linked immunosorbent assay tests using Determine and Uni-Gold for children older than 18 months. ART was initiated for any children younger than 6 years with a CD4 cell percentage of <15%, any child older than 6 years with a CD4 count <200 cells/mm^3, and all children with World Health Organization clinical stages 3 or 4 or CDC stage C. The standard initial ART regimens used were zidovudine/lamivudine/nevirapine for those weighing <10 kg or stavudine/lamivudine/nevirapine for those weighing >10 kg. Adherence counseling and education about the antiretroviral drugs were provided during the clinic session in which ART was initiated. The adherence counseling is done by clinicians (physicians or clinical officers) or designated, trained adherence nursing or pharmacy staff. Although there is some variability in the personnel providing the counseling, training in standardized adherence counseling and the use of standardized forms for assessment and counseling provides consistency among the network of AMPATH clinics. Standard elements of AMPATH adherence assessment and counseling include characterizing socioeconomic and medical status, assessing knowledge of HIV and opportunistic infections, and identifying barriers to adherence. AMPATH adherence materials are available on request from the authors. Children started on ART were seen 2 weeks after initiation of therapy and then every month thereafter. During these visits, patients underwent both clinical assessments and adherence

assessments through caregiver or self-report and received a monthly supply of antiretroviral medications.

Data Collection and Measures

ART Adherence

Clinicians complete standard encounter forms at all AMPATH clinic visits (http://amrs.iukenya.org/download/forms). The initial encounter form includes demographics, medical history, medication history, dietary intake, social history, physical exam, and laboratory data. On return visit encounter forms, the clinician collects follow-up data, including interval symptoms, medication adherence, new diagnoses, laboratory data, and modifications in drug regimens. Dedicated data entry clerks enter this information into the AMPATH Medical Record System, with data entry validated by random review of 10% of the data entered.

A standard caregiver- or self-report of adherence to ART was added to the return visit form for children in June, 2003, allowing assessment of adherence at every visit. The outcome variable of ART adherence was evaluated from data collected from responses to the question, "During the last 7 days, how many doses of his/her antiretroviral medicines did the patient take?" The options are "none," "few," "half," "most," and "all." The clinician asks this question of the child's caregiver (proxy report) unless the child is alone or the caregiver reports that the child is primarily responsible for taking his/her own medicines, in which case the child is asked directly (self-report).

In this analysis, ART adherence was defined as a binomial variable of "imperfect" vs. "perfect" adherence. Patients with imperfect ART adherence (subsequently described as "ART nonadherence") had one visit or more where adherence was not reported as "all" doses taken during the past 7 days (or >0 reports of nonadherence). This could include any report of taking "none," "few," "half," or "most" of their doses. In total, 9.3% of the children on ART had no adherence measurements and thus were excluded from analyses.

Clinic Adherence

Adherence to routine clinic visits was captured using appointment data from our electronic medical record system. The number of missed visits after starting ART was compared with the number of scheduled visits to generate a percentage of missed visits during the time period that the child has been on ART. Missed visits were defined as going for more than 35 days without a clinic visit. The percentages of missed clinic visits were categorized into 0%, 1%–9%, 10%–19%, 20%–49%, and ≥50% missed visits. Similar to ART adherence, in multivariable analyses, clinic adherence was defined as a binomial variable with "perfect" clinic adherence vs. "imperfect" clinic adherence. Imperfect clinic adherence or clinic nonadherence was defined as the child having ever missed a clinic appointment.

Orphan Status

Assessment of orphan status was done for all children at the initial visit, at which the following questions are asked: "Orphaned? (Yes/No)" "Parent deceased? Mother (Yes/No), Father (Yes/No)." For our primary analyses, orphan status was categorically defined as "neither parent dead" (referent), "only father dead," "only mother dead," or "both parents dead." We subsequently tested additional definitions for orphan status, including a binomial definition in which "orphans" were defined as those who had lost both biological parents (vs. those with neither or only one parent dead) and a different categorical definition in which children had "neither parent dead," "one parent dead (mother or father)," or "both parents dead."

Covariates

Other independent variables were selected from the domains of demographic, household, and clinical care information, including child's age, gender, and whether the child received care in the urban referral clinic or in one of the outlying outpatient clinics.

Analyses

We performed multivariable logistic regression to assess the independent association between orphan status and odds of ART nonadherence, adjusting for sex, age, clinic site, number of adherence measurements, and duration of ART treatment. In addition, we performed multivariable logistic regression to assess the independent association between orphan status and odds of ART nonadherence using varying definitions of orphanhood. Stratified analyses were also done to determine whether the association between orphan status and ART nonadherence differed by age, ART duration, and imperfect clinic adherence, adjusting for covariates. We tested statistical significance of interactions using likelihood ratio tests. Finally, we performed multivariable logistic regression to assess the independent association between orphan status, age, urban clinic setting, number of adherence measurements, or duration of ART and odds of clinic nonadherence. All models calculated 95% confidence intervals (CIs) based on robust variance estimates. All statistical analyses were performed using Stata/SE 9.2 for Windows (Stata Corp, College Station, TX).

RESULTS

In Table 1, we present the characteristics of the sample population (N = 1516), including age, gender, urban vs. outlying clinic visit, number of adherence measures, and duration on ART. These characteristics are described for the overall study population and stratified by orphan status (Table 1). The majority of the children (58%) had been on ART for less than 12 months. Sixty-nine percent had 6 or more measures of adherence recorded within the database. Orphan status was highly prevalent among the children in the AMPATH clinical care system; only 33% of children had both parents living at the time of their clinic enrollment. Children with their mothers dead or with both parents dead tended to be older at enrollment than children with neither parent dead or only their father dead (Table 1).

ART Nonadherence

Of the 1516 children, 29% (N = 445) reported ART nonadherence, with nonadherence defined as some report of

TABLE 1. Patient Characteristics Overall and Stratified by Orphan Status

	Overall (%)	Orphan Status (%)			
		Neither Parent Dead	Only Father Dead	Only Mother Dead	Mother and Father Dead
N=(%)	1516	499 (33)	319 (21)	425 (28)	273 (18)
Age (yrs)					
<1	2	4	5	1	1
1–2	18	26	26	8	5
3–5	29	33	32	27	20
6–8	24	19	20	30	29
9–11	18	12	13	23	27
12–14	9	6	4	11	18
Male	52	54	49	49	55
Urban referral clinic (vs. outlying)	14	15	13	14	14
Number of adherence measures					
1	7	8	7	6	5
2–5	24	28	24	21	23
6+	69	64	69	73	72
Duration on ART (mos)					
0–5	24	29	22	22	22
6–11	34	32	37	33	37
12–17	12	12	13	11	10
18–23	12	11	14	12	12
24–45	18	16	14	22	19

any missed doses of medication given during any of their visits (Table 2). Thus, the majority of children, 71%, sustained ART adherence based on proxy or self-report. There were few differences in demographic characteristics between children who were adherent vs. nonadherent, both for ART non-adherence and clinic adherence.

The odds of ART nonadherence increased for children who had both parents dead (OR = 1.48; 95% CI: 1.04 to 2.10), children with longer duration of ART, and those with 6 or more adherence measurements (Table 3). In contrast to these findings, children with only their father dead and children with only their mother dead did not have significantly increased odds of ART nonadherence. Other variables, including gender of the child and where the child received care, were not significantly associated with ART nonadherence.

To further investigate the association between orphan status and ART nonadherence, we performed ad hoc analyses using varying definitions of orphan status. When comparing children with neither parent dead to children with either one of their parents dead and to those with both parents dead, only the children with both parents dead had significantly increased odds of ART nonadherence (OR = 1.48; 95% CI: 1.05 to 2.09). When defining orphanhood only as having both parents dead, the odds of ART nonadherence increased significantly with the death of both parents (OR = 1.40; 95% CI: 1.05 to 1.89).

There were no significant interactions between time on ART and orphan status, between clinic adherence and orphan status, or between age and time on ART in relation to ART nonadherence. The number of adherence measures did have a significant effect on the odds of nonadherence, even when stratified by duration of time on ART. Those with less than 6 adherence measurements at more than 6 months of therapy

were more likely to be adherent. There was some evidence of an interaction between orphan status and age, with the youngest orphans having the highest odds of ART non-adherence, but this interaction had marginal significance (*P* value = 0.08). Of the 1516 children, only 56 changed to second-line regimens during the study time period. Analyses using only the visits during which all children were on the first-line ART regimen did not change the odds ratios or significance levels for the variables reported above, and thus results for all children are presented below.

Clinic Nonadherence

Over half of the children missed at least one scheduled monthly clinic visit (Table 2). Of those missing at least one clinic visit, 76% missed 1%–9% of their scheduled visits, 19% missed 10%–19%, 18% missed 20%–49%, and 5% missed >50% of their scheduled visits. Forty-one percent had missed more than 10% of their scheduled clinic visits. The percentage of children missing scheduled visits increased dramatically as the duration of ART increased, with much of the drop occurring after 6 months on ART (Table 2).

Clinic nonadherence had very different patterns of associations with orphan status and other covariates compared with ART nonadherence. Orphan status was not significantly associated with imperfect adherence in the clinic nonadher-ence model (Table 4). The odds of clinic nonadherence increased for children attending the urban referral clinic (OR = 1.85; 95% CI: 1.13 to 3.02), with longer duration on ART and with 6 or more adherence measurements (Table 4). As in the ART nonadherence models, the associations between clinic nonadherence and age or gender were not statistically significant.

TABLE 2. Demographics and ART Duration for Patients Reporting Nonadherence

	ART Nonadherent Population (%)	Clinic Nonadherent Population (%)
N (%)	445 (29)	861 (57)
Orphan status		
Neither parent dead	127 (29)	266 (31)
Only father dead	82 (18)	189 (22)
Only mother dead	136 (31)	248 (29)
Both parents dead	100 (22)	158 (18)
Age (yrs)		
<1	10 (2)	21 (2)
1–2	59 (13)	143 (17)
3–5	131 (29)	261 (30)
6–8	113 (25)	199 (23)
9–11	88 (20)	174 (20)
12–14	44 (10)	63 (7)
Male	237 (53)	441 (51)
Urban referral clinic (vs. outlying clinic)	83 (19)	177 (21)
Number of adherence measures		
1	7 (2)	13 (2)
2–5	57 (12)	117 (13)
6+	381 (86)	731 (85)
Duration on ART (mos)		
0–5	49 (11)	64 (7)
6–11	142 (32)	282 (33)
12–17	57 (13)	135 (16)
18–23	72 (16)	139 (16)
24–45	125 (28)	241 (28)

TABLE 3. Adjusted Odds of ART Nonadherence by Demographics and ART Duration

	ART Nonadherence		
	OR	95% CI	
Orphan status			
Neither parent dead	1	Reference	
Only father dead	0.96	0.68	1.34
Only mother dead	1.15	0.85	1.56
Both parents dead	**1.48**	**1.04**	**2.10**
Age (yrs)			
0–2	100	Reference	
3–11	1.36	0.99	1.88
12–14	1.37	0.85	2.20
Male	1.08	0.86	1.37
Urban referral clinic (vs. outlying clinic)	0.99	0.71	1.38
Duration on ART (mos)			
0–5	100	Reference	
6–11	1.33	0.84	2.11
12–17	**1.81**	**1.07**	**3.06**
18–23	**2.26**	**1.34**	**3.81**
24–45	**2.80**	**1.69**	**4.62**
Number of adherence measurements			
0–5	**0.41**	**0.28**	**0.69**
6 or more	1	Reference	

Bold items indicate that results are significant with P <0.05.

we found that the death of both parents was associated with significantly increased odds of ART nonadherence. This was independent of many other factors that could affect a child's adherence to ART, such as age, gender, urban vs. rural setting,

TABLE 4. Adjusted Odds of Clinic Nonadherence by Demographics and ART Duration

	Clinic Nonadherence		
	OR	95% CI	
Orphan status			
Neither parent dead	1	Reference	
Only father dead	1.15	0.81	1.63
Only mother dead	0.94	0.67	
Both parents dead	1.02	0.70	
Age (yrs)			
0–2	1.00	Reference	
3–11	1.22	0.89	
12–14	1.27	0.73	
Male	0.94	0.73	1.21
Urban referral clinic (vs. outlying clinic)	**1.85**	**1.13**	**3.02**
Duration on ART (mos)			
0–5	1.00	Reference	
6–11	**4.01**	**2.72**	**5.93**
12–17	**11.96**	**7.18**	**19.92**
18–23	**10.32**	**6.05**	**17.62**
24–45	**24.96**	**14.08**	**44.25**
Number of adherence measurement			
0–5	**0.6**	**0.42**	**0.87**
6 or more	1	Reference	

Bold items indicate that results are significant with P <0.05.

Missing Data

For <10% of children missing adherence measurements, data were not missing at random and represented children who were younger, had been on ART for a shorter duration (the majority less than 3 months), and more often had both parents alive. To assess the sensitivity of our models to these missing data, regression analyses were run including all children with missing adherence data as nonadherent and then as adherent. Although the contextual factors were not significant for the extreme "nonadherent" group, the negative association of ART nonadherence to contextual factors such as orphanhood remained, with similar odds ratios. Analyzing the missing data as "adherent" yielded stronger associations, with smaller *P* values. Although the statistical significance was sensitive to how the missing data were categorized, the relationships with contextual factors remained similar.

DISCUSSION

Overall, combined self- and proxy reports suggested that the majority of HIV-infected children receiving care in a large treatment program in Western Kenya had perfect ART adherence. ART adherence within this pediatric population was consistent with adult ART adherence estimates from resource-limited settings but higher than adherence estimates from resource-rich settings. When orphan status was examined based on whether the mother, father, or both parents were dead,

and the length of time the child had been taking ART. Clinic adherence was significantly less among this population with over half of patients missing at least one monthly visit. Unlike ART adherence, clinic adherence was not associated with any measure of orphan status, suggesting different mechanisms by which orphan status may influence HIV care. The results of this retrospective analysis reveal the importance of further investigation into the complex context in which children live and take their medicines in resource-limited settings.

The AMPATH pediatric population represents one of the largest cohorts of HIV-infected children receiving care in East Africa and thus provides an excellent opportunity to examine the reported pediatric adherence behaviors within the type of resource-limited setting in which most of the world's HIV-infected children live and receive their medical care. A majority of the pediatric patients in this cohort were adherent to ART on self- or caregiver reports; 71% had perfect adherence on all reported measures. This estimate is consistent with the pooled estimate of measured adherence among African adults of 77%.[42] This adherence estimate is higher than the majority of caregiver reports and self-reports of pediatric adherence presented in the most recent systematic review, where pediatric adherence estimates ranged from 34% to 100% and 20% to 58%, respectively.[9] The higher levels of adherence in our population could reflect the dramatic improvements in health experienced by these children as they initiate therapy. In addition, most of their families have not yet experienced long-term adverse effects from ART.

This retrospective analysis reveals a clinical population with a very high degree of orphanhood. Whereas a previous cross-sectional study involving 1190 children in Western Kenya found that 7.9% of the children had lost one or both of their parents,[25] 66% of the children receiving ART within our care system have lost one or both of their parents. Certainly, more orphans would be expected in an HIV-infected population requiring ART; however, the extent of orphanhood surpasses even estimates from other HIV treatment programs in Africa, where 15%–48% of HIV-infected children were reported to have lost one or both parents.[12,14,43,44] Furthermore, our study may actually underestimate the prevalence of orphanhood because the data regarding orphan status were documented only at the child's first visit to clinic. These findings highlight that the increasingly vulnerable population of children who receive care as HIV treatment programs such as AMPATH scale up over time.

The high prevalence of orphanhood within our clinical cohort bears particular attention because losing both parents is significantly associated with increased odds of ART nonadherence. These findings differ from previous studies done in smaller cohorts within resource-limited settings, in which orphan status was not significantly associated with ART nonadherence.[13,16,33,34] These findings also differ from results of studies done in the United States and Europe where having a foster parent or nonbiological caregiver is associated with a higher rate of ART adherence.[45–47] However, having a foster parent or nonbiological caregiver in the United States or Europe may reflect a situation in which a parent is unable to provide adequate care, rather than a situation where the parent is dead. These varying findings highlight the importance of

understanding the specific context of the caregiving situation for HIV-infected children. The findings of this study also point to the importance of distinguishing between having both parents dead and having one parent dead. There may be an additive or synergistic effect from the death of not just 1, but 2 parents. In contrast, the death of either the mother or the father alone behaved much more like having neither parent dead in our models for nonadherence. Given these findings, one must reconsider the current, most widely accepted definition of an orphan, defined as a child who has lost one or both parents through death and generally not specifying which parent has died or if both parents have died.[48] In addition, it would be important to assess the impact of how long the child has been an orphan and the impact of the age of the child during this period of orphanhood. Finally, for any of these orphan states, substantial variability in the child's social, physical, and economic environment likely exists. Our analyses point to the need to examine more carefully the specific contexts of orphanhood to better target those at greatest risk for nonadherence and other poor outcomes.

In contrast to nonadherence to ART, nonadherence to clinic visits was not significantly associated with orphan status. Although orphaned children are reported to miss their medications more frequently, they do not come for clinic visits less often than nonorphaned children in our population. Although clinic nonadherence could be suspected as a mediator of ART nonadherence for orphans, there was no evidence of such mediation on logistic regression models including clinic nonadherence. This raises several important considerations. First, it is possible that a reporting bias may be present. Nonparent caregivers may be more willing than parent caregivers to disclose when the child has missed doses of their medicines. Contextual reasons, particularly related to stigma and disclosure and how these differ by caregiver, need to be studied further. In addition, more objective measures of adherence such as pill counts, electronic dose monitoring (eg, Medication Event Monitoring Systems [MEMS] caps), or plasma drug levels could be used to validate caregiver reports. Second, there may be additional reasons for the caregivers of orphans to adhere to clinic visits even if they are not adhering to the medication. In the AMPATH care system, where clinic attendance grants not only access to ART but also food supplementation and other social supports, there may be different mechanisms which contribute to clinic and ART nonadherence among families or guardians caring for orphans. The role of social support programs or nutritional supplementation, particularly for families caring for orphans and vulnerable children, thus merits further investigation. Finally, these findings underscore that clinic nonadherence is not a perfect proxy for medication nonadherence, despite its use as a measure of ART nonadherence in some studies.[46, 49–51]

This study has several limitations that require consideration. First, our data for orphan status are cross-sectional, collected at the first visit only, which precludes us from making causal inferences. However, as discussed above, it is plausible that the death of both parents leads to a social and family setting in which it is more difficult to maintain adherence to a complicated medication regimen. Also, we may have underestimated the prevalence of orphanhood by using

only the initial data, thus biasing our results toward the null. Despite this, orphan status remained significantly associated with ART nonadherence. In addition, we could not assess the impact of duration or timing of orphan status on adherence because all the orphans in this cohort had been orphaned for the entire duration of the analysis. Second, the data on adherence came from parental, caregiver, or self-reports, depending on who accompanied the child and claimed responsibility for the medications. Our database did not allow specification of who made the adherence report, similar to several other studies from resource-limited settings.[13,14,16,17,20,52] We also do not have other measures of adherence, such as pill counts, that could validate the reported results. Although proxy or self-report is the most widely used method of adherence assessment, these reports tend to overestimate adherence[9] and are not consistently associated with pediatric clinical outcomes.[6,45,53–60] However, the majority of pediatric HIV centers rely on self- or proxy-reported measures alone,[9] indicating the need to determine the accuracy of these low-cost assessments. Effort should be made to develop and evaluate reliable, valid adherence measurement instruments for these populations. Furthermore, in this cross-sectional analysis, we did not evaluate the relationship of clinical outcomes such as CD4 counts or percentages to the self- or proxy reports. Such a comparison would not necessarily validate our reports of adherence given that proxy- or self-report methods are not consistently associated with pediatric clinical outcomes in other studies using these methods.[6,45,53–60] Our study may also underestimate the extent of ART nonadherence because it was based on clinic assessments and thus compounded by clinic nonadherence. Although patients may have some extra medication supplies and should report nonadherence from missed visits during their subsequent visits, the clinic-based ART assessments likely underestimate ART nonadherence. Finally, our data were limited to the information populated in the pediatric electronic medical record. Variables of potential importance, such as orphan care setting and caregiver's HIV status, were not available. However, the variables related to orphan status had few missing data and demonstrated a consistent association with ART adherence. In addition, less than 10% of the ART adherence data were missing. In sensitivity analyses, ART nonadherence demonstrated consistent associations with orphan status.

Because orphan status is associated with increased odds of ART nonadherence, future interventions to increase ART medication adherence should carefully consider orphan status. Careful study of how the death of one or both parents mediates and interacts with pediatric adherence and how these effects can be modified is urgently needed. Other parental, familial, or social determinants of the child's context may play important roles in mediating ART adherence. This study provides further evidence that investigating familial and society factors is crucially important to supporting care in the resource-limited settings in which most HIV-infected children live.

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