Outcomes of HIV-Infected Orphaned and Non-Orphaned Children on Antiretroviral Therapy in Western Kenya

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Objectives: Determine outcome differences between orphaned and non-orphaned children receiving antiretroviral therapy (ART).

Design: Retrospective review of prospectively recorded electronic data.

Setting: Nine HIV clinics in western Kenya.

Population: 279 children on ART enrolled between August 2002 and February 2005.

Main Measures: Orphan status, CD4%, sex- and age-adjusted height (HAZ) and weight (WAZ) *z* scores, ART adherence, mortality.

Results: Median follow-up was 34 months. Cohort included 51% males and 54% orphans. At ART initiation (baseline), 71% of children had CDC clinical stage B or C disease. Median CD4% was 9% and increased dramatically the first 30 weeks of therapy, then leveled off. Parents and guardians reported perfect adherence at every visit for 75% of children. Adherence and orphan status were not significantly associated with CD4% response. Adjusted for baseline age, follow-up was significantly shorter among orphaned children (median 33 vs. 41 weeks, $P = 0.096$). One-year mortality was 7.1% for orphaned and 6.6% for non-orphaned children ($P = 0.836$). HAZ and WAZ were significantly below norm in both groups. With ART, HAZ remained stable, while WAZ tended to increase toward the norm, especially among non-orphans. Orphans showed identical weight gains as non-orphans the first 70 weeks after start of ART but experienced reductions afterwards.

Conclusions: Good ART adherence is possible in western rural Kenya. ART for HIV-infected children produced substantial and sustainable CD4% improvement. Orphan status was not associated with worse short-term outcomes but may be a factor for long-term therapy response. ART alone may not be sufficient to reverse significant developmental lags in the HIV-positive pediatric population.

Key Words: HIV, Western Kenya, antiretroviral therapy, children, orphan

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Over 25 million adults and 1.9 million children are infected with HIV in sub-Saharan Africa, with an average prevalence of 7.5%.[1] In Kenya, 1.2 million of Kenya's 29.5 million people are currently infected with HIV, and over 100,000 of those are children.[1] In addition, 650,000 Kenyan children have been orphaned due to this disease. HIV infection is 1 of the top 5 causes of mortality in Kenya, greatly contributing to the rise in infant mortality seen in the last decade, from 50 per 1000 in the pre-AIDS era to over 77 per 1000 in 2003.[2] In addition, mortality rates for children under 5 years of age has increased from 110 to 115 per 1000. This is mainly as a result of increased cases of pneumonia and diarrheal illnesses among the HIV-infected children and those who are orphaned and therefore unable to access appropriate nutrition and health care.[1]

HIV-related symptoms and signs are rarely present at birth but develop over subsequent months or years[3–5] in about a quarter of infected children. Left untreated, HIV infection progresses rapidly to AIDS or death in the first year.[3–7] In the remainder, it progresses more slowly, with less than a quarter expected to survive beyond 8 years.[8]

Substantial declines have been observed in HIV-related morbidity due to the combined effects of access to ART and prophylaxis for opportunistic infections.[9,10] Large studies detect improvements in growth that are attributable to protease inhibitor use.[11] Improvements in height and weight gain are greatest among "responders," especially those with high viral load.[11,12]

Despite the efficacy of ART in several reports from the US and Europe, however, in Kenya, only ~75,000 adults and children are on ART out of an eligible population of more than 240,000.[2] Less than a tenth of these are children. The impact of ART on disease progression and outcomes in African children has not been adequately studied in larger cohorts treated in public health centers.

In 2001, Moi University joined with Kenya's second-largest national referral hospital, Moi Teaching and Referral

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This study and its findings are original work and have not been presented or published elsewhere

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Hospital, and Indiana University to establish the Academic Model for the Prevention and Treatment of HIV-AIDS (AMPATH).[13] AMPATH's missions are to (1) provide high-quality patient care, (2) educate patients and health care providers, and (3) establish a laboratory for clinical research in HIV/AIDS. Between November 2001 and March 2005, AMPATH became the largest HIV/AIDS care program in Kenya, enrolling 10,000 HIV-infected patients, including 1442 children. Those meeting WHO criteria received ART, funded by a variety of mechanisms but mainly by the Presidential Emergency Plan for AIDS Relief (http://www.usaid.gov/our_work/global_health/aids/pepfarfact.html). One of our hypotheses was that, due to social constraints, orphans would have greater barriers to care and hence lower adherence to clinic visits and ART, leading to lower rises in CD4% and less response in developmental indices, such as weight and height, and lesser survival. This report describes the first 279 children started on ART at the 9 AMPATH sites.

METHODS

Study Design

This study was approved by the Institutional Research and Ethics Committee of the Moi University Faculty of Health Sciences (Eldoret, Kenya) and the Institutional Review Board of the Indiana University School of Medicine (Indianapolis, IN). This cohort study used prospectively collected de-identified data stored in the computerized medical records of pediatric patients enrolled in the AMPATH clinics.

Study Population

Patients were eligible for study if they were enrolled at any one of the nine AMPATH clinic sites from August 2002 to February 29, 2005 and were initiated on ART. The urban clinic is located at Moi Teaching and Referral Hospital (MTRH). It is the hospital that is home to the Moi University Faculty of Health Sciences (MUFHS), the second-largest medical school in Kenya. It is one the first hospitals to start family-based management of HIV-infected and HIV-affected people in Kenya; with affiliated hospitals and health centers, more than 18,000 HIV infected patients with 2701 children are being followed in special outpatient HIV clinics.

At the time of this report, MTRH in urban Eldoret (Kenya's fifth-largest city) conducted 10 half-day pediatric clinic sessions per week. Half of these sessions were attended by both pediatricians and clinical officers, while the other half were managed by clinical officers and medical officers with 24-hour telephone access to the pediatrician on call. The other outpatient AMPATH clinics are rural, located in 2 district hospitals (Webuye and Teso) and health centers (Naitiri and Amukura) in Kenya's Western province, 1 in Nyanza province (Chulaimbo), and 3 in Rift Valley province (Mosoriot, Burnt Forest, and Turbo). These rural HIV clinics also hosted one or more pediatric sessions per week, some attended by a pediatrician and clinical officers and others by medical and clinical officers.

Clinical Procedures

Protocols consistent with World Health Organization (WHO) guidelines (http://www.who.int/hiv/topics/arv/en/scaling_exe_summary.pdf) for the treatment of HIV-infected pediatric patients were developed locally and followed for the duration of the study. All HIV-exposed children <1 year of age and all HIV-infected children with a CD4% of $<25\%$ were started on *Pneumocystis* prophylaxis with cotrimoxazole. HIV infection was documented by DNA-PCR (Amplicor, Roche, Basel, Switzerland) for children younger than 18 months and by 2 parallel HIV rapid ELISA tests using Determine and Unigold for children older than 18 months. Indications for initiating ART included any child <6 years of age with a CD4 cell percentage of $<15\%$, any child over 6 years of age with a CD4 count <200 cells/mm^3, and all children with WHO clinical stage of 2 and 3 (now 3 and 4) or CDC stage C. The standard initial ART regimens used at this site were zidovudine/lamuvidine/nevirapine for those weighing <10 kg or stavudine/lamuvidine/nevirapine for those weighing >10 kg. Adherence counseling and education about the antiretroviral drugs was provided to the adult or older child who accompanied the patient during the clinic session in which ART was initiated. Patients receiving ART were seen 2 weeks after initiation of therapy and then every month thereafter. During these visits, patients underwent clinical and adherence assessments and were dispensed antiretroviral drugs. Laboratory testing for HIV-infected children was based on local protocols and clinical necessity. Per protocol, a complete blood count and alanine aminotransferase and creatinine values were performed at baseline and then every 3 months. CD4 cell counts and percentages were obtained at baseline and then every 6 months. A confirmed decline in CD4 cell percentage of at least 5% in children under 6 years of age or $>50\%$ decline from peak CD4 cell count for children ages 6 and above was considered a regimen failure and triggered a change in the patient's ART regimen. Mortality data was passively collected by the study, while data on patients admitted to MTRH was actively collected. Loss to follow-up was identified when the patients failed to show up for their appointments, defined as more than 1 month after expected date of revisit for the children on ART. There was no data entry to capture this, so we depended on the appointment dates. Once there was loss to follow-up, information on mortality was collaborated with either inpatient admissions/mortality or information to the clinicians from parents (usually when they came back for own appointments) or guardians of the children. At the time of this report, there was no active routine tracking of patients who did not return for scheduled HIV clinic visits.

Data Collection and Management

Clinicians completed standard initial and return encounter forms at all AMPATH clinic visits (http://amrs.iukenya.org/download/forms). The initial encounter form included standard demographic, historical (including birth history and maternal prophylaxis), dietary intake, social, physical, and laboratory data as well as medications provided (antiretroviral drugs and opportunistic infection prophylaxis). Follow-up data were collected on intercurrent symptoms, medication adherence, new diagnosis, laboratory data, and modifications in drug regimens. Dedicated data-entry clerks entered this information into the

AMPATH Medical Record System, which uses an MS-Access Database (Microsoft Corp., Redmond, WA).[14]

Two medication-adherence questions were asked during all return visits: (1) during the last month, has the patient missed any medications (yes/no response, with the category of any missing medications—ART, *Pneumocystis* prophylaxis, tuberculosis prophylaxis, tuberculosis treatment—selected with check boxes), and (2) during the past 7 days, how many of his/her pills did the patient take (none, few, half, most, all).

Drug-adherence history was largely provided by caregivers who included parents, siblings, grandparents, other relatives, and guardians. On several occasions, the person who administered the medication to the child did not accompany the child to the clinic, making the reported adherence potentially unreliable. This information was supplemented, however, by performing pill counts for those using tablets and capsules and estimating remaining volumes for those using syrups. The clinician's impression was also included in assigning a qualitative estimate of adherence.

Statistical Methods

A P value of <0.05 was considered significant in all analyses. Descriptive statistics, such as frequencies, medians, and 95% nonparametric confidence intervals (observations corresponding to the 2.5th and 97.5th percentiles) or interquartile ranges (observations corresponding to the 25% and 75% percentile), are presented, and no assumptions on the underlying data distribution are made unless absolutely necessary. When such assumptions cannot be avoided, they are described in the text. Associations between categorical factors were assessed through the 2-sided Fisher's exact test. Simple 1-way comparisons of continuous outcomes between groups were performed by the Kruskal-Wallis test.

Analysis of duration of follow-up was performed by the method of Kaplan and Meier. Data from patients still under observation were terminated as of February 29, 2005. Children confirmed to be dead or lost to follow-up were considered censored for purposes of follow-up as of their confirmed date of death or their last recorded visit, respectively. Confidence intervals for the median duration of follow-up were produced via Greenwood's formula of the variance of the Kaplan-Meier estimate. Analyses of duration of follow-up adjusted for age were performed via the Cox proportional hazards model and tested the statistical hypotheses via the Wald test.

Longitudinal analyses of CD4 cell percent and sex- and age-adjusted z scores for weight (WAZ) and height (HAZ) were based on mixed-effects models.[15] We fit a piece-wise linear (change point) model to the log-transformed CD4 cell percent levels over time to account for the observation that CD4 cell percent rose rapidly for a period after initiation of antiviral therapy and stabilized thereafter. The optimum time between the rapid early phase and the stable later phase of CD4 cell percent was estimated statistically. A number of additional predictors of CD4 cell percent change were considered. The significance of each predictor's explanatory ability on CD4 cell percent changes was assessed through Wald tests. A similar change point model was applied to the weight z score data. A simpler longitudinal mixed model (without a change point) was applied to the height z scores. All analyses were performed with the SAS system, version 9 (SAS Institute, Cary, NC). WAZ and HAZ scores were calculated via Epi-Info, version 2002 (Centers for Disease Control and Prevention, Atlanta, GA) and correspond to CDC 2000 specifications.[16,17]

RESULTS

Patient Characteristics

Data were available for 279 children who received ART out of 1353 HIV-infected children who were followed from December 12, 2001, to February 29, 2005. These 279 children had 3354 patient visits (median number of visits for each child 10 visits, 95% CI: 2 to 34 visits), and the median duration of follow-up was 34 weeks (95% CI: 27 to 39). The majority of patients were enrolled at the outpatient HIV clinic at the urban outpatient clinic of MTRH (63%), with the remaining patients enrolled at district hospitals and rural health centers (Table 1). The median age at ART initiation was 6 years (CI 4.8 months to 13.7 years). Among children receiving ART, 7.4% were <1 year of age at start of ART therapy, 34% were between 1 and 5 years old, and 58.6% were older than 5 years. About half of the children were boys (51%), and a little more than half (54%) were orphaned (had experienced the death of their mother or both parents).

At enrollment, approximately 10% of children were reported to have delayed developmental milestones, and approximately one-third had experienced weight loss. Rash, fever, fatigue, vomiting, and headache were also reported symptoms at enrollment (Table 2). At the time of ART initiation, the majority of children (75%) were identified as having CDC clinical stage B or C. The median CD4 cell count at ART initiation was 176 cells/mL (CI 4 to 1356) and the median CD4% was 9% (CI: 1% to 38%; Table 3).

Just over 75% of children and/or their accompanying caregivers reported perfect adherence to ART on every visit, as assessed by the clinician. Only 3 patients (1%) required a change to a second-line regimen due to failure based on clinical and immunological parameters. There were 10 documented deaths, and 32 (11%) patients were lost to follow-up during the study period.

Characteristics of Orphaned Children

Orphaned status was associated with slightly shorter median duration of follow-up, 33 versus 41 weeks, respectively ($P = 0.096$). Orphans were older than non-orphans at initiation of ART, a median of 8.3 versus 4.7 years of age, respectively ($P < 0.001$). There was no significant difference in the proportion of orphaned children identified as symptomatic (CDC clinical stage B or C) when compared to non-orphaned children, 70.8% versus 74.7%, respectively ($P = 0.593$). The median CD4 cell percentage measured closest to the time of ART initiation was 10% for orphans and was not significantly different from non-orphaned children (9%; $P = 0.819$). Perfect adherence among children with known orphan status was 75% and was not significantly different between orphaned and non-orphaned children, 73% versus 71%,

TABLE 1. Demographic and Enrollment Information

	N = 279
Sex	
Male	142 (50.9%)
Female	137 (49.1%)
Tribe	
Kalenjin/Nandi	100 (36.4%)
Luo	38 (13.8%)
Luhya	69 (25.1%)
Kisii	8 (2.9%)
Kikuyu	43 (15.6%)
Other	17 (6.2%)
Missing	4
Clinic	
MTRH	175 (62.7%)
MRHC	37 (13.3%)
Turbo	18 (6.5%)
Burnt Forest	11 (3.9%)
Distant clinics	38 (13.6%)
Orphaned status	
Orphaned	106 (53.8%)
Not orphaned	91 (46.2%)
Missing	82
Number of siblings	
0	18 (8.1%)
1	55 (24.9%)
2	56 (25.3%)
3	39 (17.7%)
4	24 (10.9%)
5	16 (7.2%)
>6	13 (6.1%)
Missing	58
School attendance*	
Yes	134 (87.6%)
No	19 (12.4%)
N/A	83
Missing	43

*Whether the child ever attended school at any level.

TABLE 2. Most Frequent Signs and Symptoms at Presentation

	N = 234
Anemia	8 (3.4%)
Delayed milestones	24 (10.3%)
Diarrhea	21 (7.7%)
Fever	99 (42.3%)
Fatigue	56 (23.9%)
Headache	19 (8.1%)
Mouth sores	31 (13.3%)
Poor appetite	51 (21.8%)
Rash	104 (44.4%)
Weight Loss	73 (31.2%)
Vomiting	39 (16.7%)

respectively ($P = 0.863$). Orphan status was not a significant predictor of death ($P = 0.836$) or loss to follow-up ($P = 0.096$).

Impact of Antiretroviral Therapy

We assessed the impact of ART on CD4%. A longitudinal mixed model was applied to log CD4% as described in the Methods. CD4% response showed a two-phase time trend (Fig. 1). The first phase was seen that was characterized by steep CD4% increases followed by a second phase where CD4% increases were much less pronounced. It was estimated that the first phase lasted about 30 weeks (Fig. 1). Using a multivariate analysis that included age, sex, orphan status, and ART adherence, only age was found to be significantly associated with CD4% fluctuations (Table 4): older children had more rapid increases in CD4 cell percentages with each additional year of age ($P = 0.019$). After adjustment for age, CD4 cell percentage increased rapidly during the first 30 weeks of ART ($P < 0.001$), with mean peaks at 30 weeks of 23.0% for orphans and 24.1% for non-orphans. CD4 cell percentage remained largely stable thereafter, neither increasing nor decreasing significantly over the remainder of the follow-up period (Table 4). Orphan status was not a significant predictor of CD4% response to ART therapy ($P = 0.694$).

Sex- and age-adjusted weight (WAZ) and height (HAZ) z score responses to ART were also analyzed (Figs. 2A and B, respectively). In terms of weight, HIV-positive children appeared to be, on average, significantly below norm. Weight increased for all children for the first 70 weeks after ART initiation ($P < 0.001$). Orphaned children were slightly lower in terms of weight z scores by about 0.260 standard deviation ($P = 0.058$) but experienced identical weight gains with non-orphaned children during the first 70 weeks post-ART initiation. After 70 weeks, weight gains remained stagnant for non-orphaned children but started to decrease significantly for orphaned children ($P = 0.002$), although data beyond 70 weeks are sparse (Fig. 2A). In terms of height, HIV-positive children were, on average, significantly below norm. Orphan children lagged significantly in terms of height compared to non-orphan children throughout the observation period by about 0.296 standard deviation ($P < 0.001$). Sex- and age-adjusted height did not increase during the period following ART initiation for either group ($P = 0.638$; Fig. 2B).

DISCUSSION

In this prospective cohort study, we demonstrated that it is possible to administer ART resulting in favorable outcomes for children in sub-Saharan Africa despite the complexity associated with pediatric dosing and formulation and important barriers to care, such as poverty and orphan status. This cohort of children showed a dramatic immunologic response to ART, as demonstrated by the rise in CD4%.

Prior research has also suggested that weight is a good clinical indicator of response to ART.[11,12,18] Although we found significant increases in sex- and age-adjusted weight after initiation of ART, the increases never overcame the developmental lag that this cohort of HIV-positive children

TABLE 3. Anthropometric and Disease-Related Indices at Initiation of Antiretroviral Therapy

	All	Orphans	Non-Orphan	*P* Value
Age (y)				<0.0001†
N	256	89	89	
Median	6.04	8.29	4.67	
95% CI*	0.4–13.7	1.7–13.7	0.4–13.7	
Weight *z* scores (WAZ)				0.4724
N	253	89	89	
Median	−2.60	−2.72	−2.48	
95% CI	−9.61–2.33	−8.69–0.11	−8.36–0.93	
Height *z* scores (HAZ)				0.5639
N	236	85	80	
Median	−2.40	−2.48	−2.44	
95% CI	−6.10–4.20	−6.23–0.16	−5.36–3.10	
CD4 percent (%)				0.8192
N	209	75	83	
Median	10%	9%	10%	
Range	1%–38%	1%–33%	1%–41%	
CD4 count (cells/mL)				0.4768
N	198	83	62	
Median	224	259	169	
Range	4–1420	4–942	4–1744	
CDC stage				0.5931‡
Total N (% B&C)	231 (71.4%)	96 (70.8%)	83 (74.7%)	

*95% non-parametric confidence interval (2.5–97.5 percentile).
†Kruskal-Wallis test.
‡Fisher's exact test.

experienced just before initiation of therapy. However, in a resource-poor environment, weight gain may be blunted by lack of access to food[2] or by comorbid conditions such as malaria. Although AMPATH has established a food-security program consisting of production and training farms, these farms were not in place during the first 3 years of the AMPATH program.[13,19] Moreover, before implementing the food security program we did not have an adequate measure of access to food or whether the patients in this study had their caloric and other nutritional needs met.

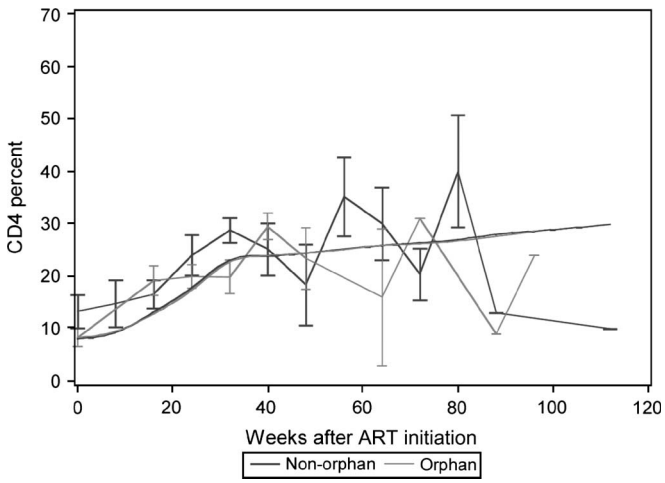

FIGURE 1. Change of CD4% over time; raw means (every 8 weeks, ±2 SD) and fitted change point model (smooth line) are shown. The change point is estimated to occur at ~30 weeks from the start of therapy.

When we analyzed the response to treatment longitudinally, a steady and statistically significant increase in CD4% was found that stabilized after 30 weeks. The average increase in CD4% over the first 30 weeks of therapy was 11%, similar to the response to ART described in pooled data by Médicins sans Frontièrs (MSF)[20] in resource-limited settings that included Africa. In the MSF cohort of 392 children on ART, the median gain in CD4% was 8.2% at 6 months (N = 48, IQR: 4.8 to 12.6) and 10.2% at 12 months (N = 12, IQR: 6.6 to 16.3) Similar increases in CD4% have been reported from Botswana (672 children in Princess Marina Hospital, Gaborone)[21] and South Africa (121 children in Red Cross Children's Hospital and 87 in Chris Hani Barangwanath Hospital).[22,23] The increase in CD4% we report compares well with observations in Europe and the US.[24–26]

We hypothesized that orphan status would impede adherence to ART and thereby blunt children's immunologic response to treatment. However, we found no effect of orphan status on ART adherence, rise in CD4%, or in sex- and age-adjusted weight and height, at least in the short term, or mortality. This possibly suggests that the Kenyan extended families functioned well and allowed family members to give adequate support to affected children, although their ability to continue caring for these children may be under threat due to rising poverty levels.[28] In addition, preliminary results of a study in a cohort of AMPATH patients looking at the

TABLE 4. Effect of Age on Log CD4 Percent Change After Start of ARV Therapy*

Effect	Estimate	SD	*P* Value
Intercept	3.184	0.094	<0.0001
Orphans	−0.050	0.125	0.6940
CD4 percent change ($t \leq 30$ weeks)	0.028	0.007	0.0004
CD4 percent increase ($t \leq 30$ weeks), for each additional year of age	0.002	0.001	0.0190
CD4 percent change ($t > 30$ weeks)	0.002	0.007	0.7498

*The log CD4 percent increases rapidly over the first 30 weeks (by an average 0.028 log unit per month) and is stable thereafter. The increase, over the first 30 weeks, is steeper for older children (by about 0.002 log CD4 percent unit for each additional year of age). There are no differences (in the first 30 weeks or afterward) between orphaned and non-orphaned children.

SD indicates standard deviation.

economic impact on families where someone is being treated for HIV/AIDS showed that such families had more disposable income than families without AIDS, with the funds being donated by family, friends, community, etc.[27] This might explain why families taking in HIV-positive orphans might have more resources, and hence no greater barriers to care, at least initially, than families with their own children infected with HIV. The lack of an effect of orphan status may also be due to selection bias, because only children with sufficient support to be brought to an AMPATH clinic for care could be included in this cohort study.

There was some evidence of weight declines in the longer term. Although this observation needs to be interpreted cautiously due to the sparsity of data, particularly in the orphan group, the developmental lags observed are worrisome and should be explored further. Regardless, these data show that early developmental lags in terms of height and weight were never overcome despite improvements after initiation of ART. This observation implies that ART alone is not sufficient to reverse significant developmental lags present in this HIV-positive pediatric population. Nutritional and social support programs may be required, and such interventions should be rigorously studied to assess their benefits and cost-effectiveness.

Adherence is a special issue in pediatrics not only because of social situations but also because many of the drugs are not child friendly. Adherence to the basic regimen—lamivudine, stavudine, and nevirapine or lamivudine, zidovudine, and nevirapine—was reported as "perfect" at all visits for 75% of the children in this cohort and did not differ significantly among orphaned or non-orphaned children. This good adherence could explain the increases in CD4% shown in this cohort. Adherence is important not only for individual patient responses to ART but also because lack of adherence to prescribed regimens and subtherapeutic levels of antiretroviral medications, particularly protease inhibitors, may enhance development of drug resistance and the likelihood of virologic failure.[28] Studies of adherence among children in Europe and the US have reported adherence rates of 40% to 70%.[24–26] Our results demonstrate that pediatric adherence with ART in a resource-constrained setting can parallel levels achieved in developed settings despite the expected constraints of reduced access and social barriers to care. The fact that there might be a difference between actual and reported adherence as given by caregivers may explain the failure of adherence that is associated with CD4 responses in this cohort.

Fewer than 1% of the children in this cohort required switching to second-line ART due to treatment failure. This is a remarkable achievement given that more than half of the cohort is orphaned children and depend on others to administer drugs. It indicates, however, that, with the reported good adherence in this cohort, it is possible to achieve good treatment outcomes. In turn, this minimizes the necessity of second-line drugs that, although available through this program, are expensive and generally inaccessible in most of sub-Saharan Africa. It also might mean that orphans are well taken care of by family members in the typical African culture that cherishes extended family relations.[28] However, the lack of relationship between adherence and CD4 response

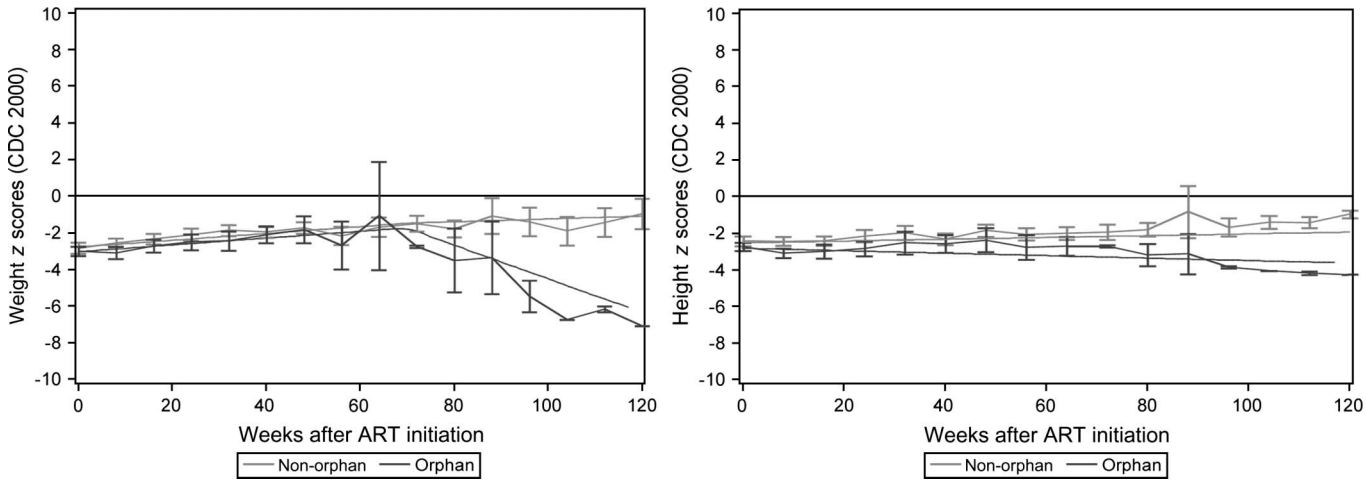

FIGURE 2. Changes of weight (left panel) and height (right panel) *z* scores after start of ART; raw means (±2 SD) and fitted values are adjusted for age and sex.

might also be an indication of some inaccuracy in the reported adherence or be limited by the size of the cohort. We do not know who among the 11% lost to follow-up while on ARVs would have been eligible for second-line ART.

The observed mortality rate is relatively low over almost 3 years of observation considering the reported death rates for children in Africa,[4] especially those with the level of advanced HIV disease seen in this cohort. However, 32 patients (11%) did not return for follow-up visits and were not hospitalized. Because there is no formal mechanism for recording deaths in Kenya, it is difficult to know how many of these patients may be dead. Hence, conclusions about death rates and predictors of death must be considered with caution. Nevertheless, the documented 5% mortality rate in our cohort is comparable to that reported by MSF in similar resource-poor environments where mortality of children receiving ART was 7.8% over a period of 40 months.[20]

Study Limitations

The study was performed in a single 9-site treatment program in western Kenya supported by the United States' Presidential Emergency Plan for AIDS Relief (PEPFAR). Our results may not be generalizable to other treatment programs in sub-Saharan Africa due the cultural differences that affect how caregivers give ARVs to their children. Also, conclusions about adherence are limited due to lack of a more robust measure of adherence. There was significant loss to follow-up, particularly among orphaned children, and therefore we might be underestimating the mortality rate and overestimating response to therapy.

CONCLUSIONS

This project has confirmed the feasibility of providing ART to children in resource-poor settings in sub-Saharan Africa. Children treated with ART within our cohort had significant improvement in CD4 cell percent, especially during the initial 30 weeks of therapy, and substantial weight gains, at least in the short term. However, HIV-positive children did not overcome developmental lags present before initiation of therapy, suggesting that ART may be only partially able to reverse significant developmental lags in the HIV-positive pediatric population.

Reported drug adherence was high, response to therapy was independent of orphan status, and mortality was low, although there was substantial loss of patient follow-up. Future research is needed on the longer-term outcomes of ART, the rate at which drug resistance occurs, how best to measure adherence to ART, and how to track patients in resource-poor settings.

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