Temporal Trends in Mortality and Loss to Follow-up Among Children Enrolled in Côte d'Ivoire's National Antiretroviral Therapy Program

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Background: During 2004–2008, >2000 children (<15 years old) initiated antiretroviral therapy (ART) in Côte d'Ivoire. Nationally representative outcomes, temporal trends in outcomes during 2004–2008 and site-level outcome determinants have not been investigated.

Methods: Incidence rates of death, loss to follow-up (LTFU) and attrition (death or LTFU) were evaluated in a nationally representative, retrospective cohort study among 2,110 children, who initiated ART at 29 facilities in Côte d'Ivoire during 2004–2008.

Results: At ART initiation, 54% were male, 1% was HIV-2-infected and median age was 5.1 years. Median CD4% was 11%, and 61% had weight-for-age Z-score (WAZ) ≤−2. Vaccination completion was documented for 9% of children. Eleven of 29 facilities had an integrated nutrition program. Over 4585 person-years of ART, 237 children died and 427 became LTFU. Twelve-month attrition was 22% overall, but increased from 4% to 34% during 2004–2008, due to increases in 12-month mortality (from 3–11%) and 12-month LTFU (from 2% to 23%). In adjusted analysis, compared with enrollees in 2004, enrollees in 2008 had nearly 4-fold higher mortality and 8-fold higher LTFU. World Health Organization stage III/IV, CD4% <10%, WAZ ≤2 and hemoglobin <8 g/dL, were predictive of mortality. Incomplete vaccination was predictive of mortality and LTFU. Facilities with nutrition programs had lower LTFU and mortality rates. Clinics reporting nurse dissatisfaction with working conditions had higher LTFU rates.

Conclusion: Investigation of causes of increasing mortality and LTFU is needed. Ensuring earlier ART initiation, vaccination completion, scale-up of site-level nutrition programs and nurse work-environment satisfaction, could improve pediatric ART program outcomes.

Key Words: pediatric antiretroviral therapy, outcomes, Côte d'Ivoire

(*Pediatr Infect Dis J* 2014;33:1134–1140)

Accepted for publication April 29, 2014.

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Presented in part at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, Italy, July 17–20, 2011 (MOPE242).

The authors have no conflicts of interest to disclose.

This research has been supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the US Centers for Disease Control and Prevention.

Use of trade names is for identification only and does not imply endorsement by the US Centers for Disease Control and Prevention or the US Department of Health and Human Services. The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention.

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ISSN: 0891-3668/14/3311-1134
DOI: 10.1097/INF.0000000000000457

In sub-Saharan Africa, about 1000 children acquire HIV daily through mother-to-child transmission,[1] and without treatment about half die before their second birthday.[2] Despite global urgency to expand antiretroviral therapy (ART) access for children, progress has been suboptimal in low-income and middle-income countries.[3] In Côte d'Ivoire, only 16% of 35,000 ART-eligible children were receiving ART by 2013,[4] compared with 55% of 190,000 ART-eligible adults.[5]

Expanding access to ART for HIV-infected children is a priority of the Ivorian Ministry of Health (MOH) and partners, including the US President's Emergency Plan for AIDS Relief (PEPFAR). Regular evaluation of ART outcomes and predictors of outcomes is important to inform policies and ensure quality care during scale-up.[6] Previous evaluations have been restricted to small cohorts in Abidjan[7,8] or cohorts managed largely by a single nongovernmental organization.[9] In addition, no previous evaluations have assessed facility-level predictors of ART outcomes or trends in outcomes over time. Therefore, we conducted a large nationally representative evaluation of the pediatric ART program, assessed temporal trends in mortality and loss to follow-up (LTFU) and evaluated facility-level determinants of these outcomes.

METHODS

Eligibility for ART

During 2004–2008, children (aged 0–14 years) diagnosed with World Health Organization (WHO) stage IV disease, WHO stage III disease while <12 months old, or WHO stage III disease with certain clinical conditions, were eligible for ART. Children not yet eligible by clinical criteria could be eligible for ART based on age-dependent CD4% or count criteria, as described in the 2006 WHO treatment guidelines.[10]

Recommended first-line ART regimens for children with HIV-1-infection include 2 nucleoside reverse transcriptase inhibitors (NRTI) and either nevirapine or efavirenz depending on the child's age. For HIV-2-infected children, 2 nucleoside reverse transcriptase inhibitors and a ritonavir-boosted protease inhibitor were recommended. ART was provided free of charge to patients through support from the government and donors, including PEPFAR.

Cotrimoxazole was recommended for all children initiating ART. Costs of non-ART drugs (eg, cotrimoxazole) were charged to the patients, although at a few facilities, nongovernmental organizations covered non-ART drug costs. Besides cotrimoxazole, there was no standard HIV care package recommended for children

initiating ART during 2004–2008. However, some facilities had funding to provide food supplementation as part of a comprehensive integrated nutrition program.[11]

Patient Monitoring

At baseline and at least every 6 months, weight measurements, clinical staging, tuberculosis screening, hemoglobin measurements and CD4% measurements were recommended to monitor disease progression or improvement. At each visit, standard MOH-recommended medical records were completed. Patients collected medications monthly from the pharmacy or, if stable on therapy, every 2–3 months.

Study Design and Study Population

This was a nationally representative retrospective cohort study. By January 1, 2008, about 3000 children had initiated ART at 64 health facilities.[12] To improve study feasibility, only facilities with >10 pediatric ART enrollees by January 1, 2008, were considered study-eligible. Of 30 eligible facilities, 29 agreed to participate. According to MOH records, these 29 facilities had enrolled 2820 (94%) of all 3000 children enrolled nationally during 1998–2008. Because medical records of ART enrollees before 2004 had considerable missing data, the protocol excluded 427 enrollees, who started treatment before 2004. A further 195 records were not found or never existed, while 88 had been transferred with the child to another facility. All remaining 2110 records were included in the study. Data were collected from the MOH-recommended medical records by trained data abstractors during November 2009 through March 2010.

Treatment Outcomes

The primary outcomes of interest were mortality and LTFU. A child was considered LTFU if he/she was absent from the facility in the 90 days preceding data abstraction, and if there was no documentation of death or transferal since the last visit. The date of the most recent visit was considered the date of LTFU. The combined outcome of attrition (death or LTFU) was a secondary outcome of interest. For all time-to-event analyses, transfers were censored from time-to-event analyses at the date of transfer.

Exposure Variables

All variables routinely collected on MOH-recommended ART records were assessed as possible predictors for death and LTFU (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966). Weight was recoded as weight-for-age Z-score (WAZ), using Centers for Disease Control and Prevention (CDC) growth curves for children aged 5–14 years, and WHO curves for children aged 0 to <5 years. A child was considered fully vaccinated if he/she had received a yellow fever vaccine, measles vaccine and 3 doses of the pentavalent diphtheria-tetanus-pertussis-polio-hepatitis (DTPPH) B vaccine, by the time of data abstraction.

At each of the 29 selected health facilities, interviews were conducted with pediatric ART program managers to gain information on site-level characteristics that were considered possible site-level attrition determinants during 2004–2008. The interviews were conducted during November 2009 through March 2010. If a site-level variable (eg, availability of on-site CD4 testing) changed over time during 2004–2008, then the program manager was asked to estimate whether the majority of children enrolled on ART at his/her facility during 2004–2008 had been exposed to the site-level variable or not.

Analytic Methods

Data were analyzed using STATA 11 (StataCorp, 2009, Stata Statistical Software, Release 11, College Station, TX).

Missing data are reported for each covariate of interest in Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966. If <30% of observations were missing data for a baseline demographic or clinical covariate of interest, multiple imputation with chained equations was used to impute the missing data.[13] The ice[14–16] procedure in STATA was used to create 20 imputed datasets for each of 2 outcomes (death and LTFU). The imputation model included the event indicator, all study variables and the Nelson–Aalen estimate of cumulative hazard.[17]

To assess the association between baseline characteristics and year of ART initiation, unadjusted linear, logistic and ordered logistic regression models, were used for continuous, binary and multilevel categorical variables, respectively.

In time-to-event analysis, with the origin set at the date of ART initiation, a competing risks model was used to estimate 12-month mortality and LTFU for each annual cohort of children starting ART during 2004–2008.

For each outcome (death and LTFU), Cox proportional hazards regression models were used to estimate adjusted hazard ratios and 95% confidence intervals (CI) for covariates of interest.[18] All patient-level covariates (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966) were considered *a priori* variables for inclusion in the multivariable model. Based on prior publications from Côte d'Ivoire, site size[19] and any ART stock-out in the preceding 12 months[20] were considered a priori facility-level variables for inclusion in the model. Other facility-level characteristics were included in the model if the *P*-value of the likelihood ratio test for significance during forward regression was <0.05. A shared frailty model was used to account for intra-facility correlation.

The proportional hazards assumption was assessed using visual methods and the Grambsch and Therneau test.[21] Estimates were combined across the imputed datasets according to Rubin's rules[13] using the mim procedure in STATA.[22] Stacked cumulative incidence curves were used to examine cumulative probability of death and LTFU over time.

Ethics Approval

This study was approved by the Ivorian Ethics Review Committee, the Institutional Review Board (IRB) of the US Centers for Disease Control and Prevention (CDC) and the Harvard School of Public Health (HSPH) IRB by September 19, 2008.

RESULTS

Baseline Characteristics

Among 2110 children at ART initiation, median age was 5.1 years, with 21% <2 years, 27% aged 2–4 years and 51% aged 5–14 years (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966). During 2004–2008, the proportion of children aged <2 years at ART initiation did not increase significantly ($P = 0.106$).

During 2004–2008, 54% of children were male (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966). At ART initiation, 34% of children were maternal orphans and 24% paternal orphans, with 46% of children having lost at least 1 parent and 12% having lost both parents. The proportion of children who had lost at least 1 parent declined from 51% to 39% during 2004–2008 ($P < 0.001$).

Documentation of completion of the DTPPH series, measles vaccine and yellow fever vaccine, was observed in 13%, 10% and 10% of records, respectively. The proportion of records documenting completion of all recommended vaccinations was 9% and this did not change significantly during 2004–2008 (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966).

Overall, 15 children were HIV-2-infected and 5 children dually HIV-1 and HIV-2 reactive (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966). During 2004–2008, 28% of ART enrollees had WHO stage IV disease, 9% had prior tuberculosis, 7% had active tuberculosis at ART initiation, 61% had a WAZ ≤−2 and 19% had a hemoglobin <8 g/dL, with these proportions not changing significantly over time (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966). Overall median baseline CD4% was 11% and this did not change significantly over time.

The proportion of children prescribed cotrimoxazole at ART initiation increased from 36% to 65% ($P < 0.001$), but the proportion prescribed suboptimal ART regimens remained relatively constant at 4–8% during 2004–2008 (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B966).

Baseline ART Regimens

The most common initial ART regimen for children <3 years included nevirapine, lamivudine and 1 of zidovudine, stavudine or didanosine (50%), while for children aged ≥3 years, the most common regimen included efavirenz, lamivudine and 1 of zidovudine, stavudine or didanosine (68%) (Table 1). Unboosted nelfinavir in combination with lamividine, and 1 of zidovudine, stavudine or didanosine was prescribed to 28% of children <3 years and 11% of children ≥3 years.

Efavirenz-containing regimens were prescribed to 106 (15%) children aged <3 years at ART initiation (Table 1). Potentially, toxic regimens were prescribed to 12 (1%) of all children. Overall, 7% of children were prescribed suboptimal regimens, with 16% of children <3 years and 2% of children ≥3 years, prescribed suboptimal regimens.

Facility-level Characteristics

Most ART facilities [21 (72%) of 29] were primary health care facilities and most [24 (83%) of 29] had enrolled ≤100 children on ART by the time of study start (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/B969, which lists all facility-level characteristics evaluated). Doctor and nurse satisfaction with working conditions were reported at 18 (62%) and 22 (76%) of 29 facilities, respectively. Eighteen (62%) of 29 facilities reported a stock-out of antiretrovirals (either first or second-line antiretrovirals) in the preceding 12 months. Eleven (38%) of 29 facilities provided an integrated nutrition program for pediatric ART enrollees.

Mortality and LTFU

Over 4585 person-years of follow-up, 664 children were lost through attrition; 237 children died and 427 became LTFU. Much of the documented death [136 (57%) of 237 events], and LTFU [149 (35%) of 427 events] occurred within days 0–90 of ART, with 43% of all attrition (286 events) occurring in this time period.

For all enrollees during 2004–2008, attrition proportions at 6, 12, 24, 36, 48 and 60 months were 17%, 22%, 27%, 32%, 37% and 41%. However, 12-month attrition increased from 4% for 2004 ART enrollees to 17%, 22%, 23% and 34% for 2005, 2006, 2007 and 2008 ART enrollees, respectively (Table 2). Increases in 12-month attrition proportions during this time period were due to increases in 12-month mortality (from 3% to 11%) and LTFU (from 2% to 23%).

Patient-level Predictors

Compared with children aged 5–14 years, children aged <2 years were more at risk of death (adjusted hazard ratio [AHR], 1.67; 95% CI, 1.15–2.43) but not LTFU (Table, Supplemental Digital Content 3, http://links.lww.com/INF/B970). Compared to children with documented vaccine schedule completion, children lacking this documentation had higher mortality (AHR, 2.88; 95% CI, 1.07–7.74) and LTFU (AHR, 1.77; 95% CI, 1.02–3.10).

Compared with children starting ART in 2004, children starting ART in 2005, 2006, 2007 and 2008 had 2.44, 2.32, 2.18 and 3.70 times the rate of documented death (Table, Supplemental Digital Content 3, http://links.lww.com/INF/B970; Fig. 1). Compared with ART enrollees in 2004, ART enrollees in 2005, 2006, 2007 and 2008 had 1.83, 3.39, 4.82 and 7.96 times higher rates of LTFU.

Compared with ART enrollees with WHO stage I/II, enrollees with WHO stage III (AHR, 2.09; 95% CI, 1.14–3.84) or IV (AHR, 2.71; 95% CI, 1.42–5.16) had increased mortality rates but not LTFU (Table, Supplemental Digital Content 3, http://links.lww.com/INF/B970). Similarly, compared with children with CD4% >20% at ART initiation, children with CD4% <10% had increased mortality (AHR, 2.51; 95% CI, 1.38–4.57) but not LTFU.

TABLE 1. Initial ART Regimens for ART Enrollees <15 Years at ART Start in Côte d'Ivoire during 2004–2008

	Age <3 years (N = 702)		Age ≥3 years (N = 1408)		All ages (N = 2110)	
Regimen Distribution	n (%)		n (%)		n (%)	
AZT/D4T/DDI+3TC+NVP	352	50%	252	18%	604	29%
AZT/D4T/DDI+3TC+EFV*	106	15%	957	68%	1,063	50%
AZT/D4T/DDI/ABC+3TC+LPV/r	31	4%	7	0.5%	38	2%
AZT/D4T+3TC+NFV/r	2	0.3%	0	0.0%	2	0%
AZT/D4T+3TC+ABC	9	1%	2	0.1%	11	1%
AZT/D4T/DDI+3TC+Unboosted NFV†	197	28%	160	11%	357	17%
Potentially Toxic Regimens‡	2	0.3%	10	1%	12	1%
Mono/Dual therapy	2	0.3%	6	0.4%	8	0%
HIV-2 or dual HIV-1 and HIV-2 Prescribed NNRTI§	0	0%	8	0.6%	8	0%
Unknown	1	0.1%	6	0.4%	7	0%
Total	702	100%	1,408	100%	2,110	100%
Overall appropriateness of regimen						
Appropriate	591	84%	1,378	98%	1,969	93%
Suboptimal¶	110	16%	24	2%	134	6%
Missing	1	0.1%	6	0.4%	7	0.3%

*EFV-containing regimens not recommended for children below 3 years of age.

†Unboosted nelfinavir (NFV) was not recommended first line therapy during 2004–2008, but was a drug option for second line regimens.

‡Potentially toxic regimens were those containing D4T and AZT or D4T and DDI.

§NNRTIs are not recommended for treatment of HIV-2 or dual HIV-1 and HIV-2 infection.

¶EFV-containing regimens for children below 3 years of age, potentially toxic regimens, mono/dual therapy, NNRTI-containing regimens for HIV-2 or dual HIV-1 and HIV-2 infection.

AZT indicates zidovudine; D4T, stavudine; DDI, didanosine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz; ABC, abacavir; LPV/r, ritonavir-boosted lopinavir; NFV/r, ritonavir-boosted nelfinavir; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor.

TABLE 2. Incidence of Death and Loss to Follow-up among Children Starting ART During 2004–2008 in Côte d'Ivoire (N = 2110)*

Years After ART Initiation	2004 (%)	2005 (%)	2006 (%)	2007 (%)	2008 (%)
Death					
0.5	1.6	8.3	9.7	7.4	9.5
1	2.7	11.1	11.1	8.1	11.2
LTFU					
0.5	1.1	3.6	9.3	12.2	13.7
1	1.6	5.5	11.1	14.7	22.6
Attrition†					
0.5	2.7	11.8	18.9	19.7	23.2
1	4.3	16.6	22.2	22.8	33.9
Retention†					
0.5	97.3	88.2	81.1	80.3	76.8
1	95.7	83.4	77.8	77.2	66.1

*Note that incidence estimates are representative of the 2110 children included in the analysis.

†Attrition is the combined cumulative incidence of death or loss to follow-up, while retention is the proportion of children remaining alive and on ART (1-attrition).

Compared with children with WAZ >−2, children with WAZ ≤−2 had increased mortality (AHR, 2.36; 95% CI, 1.61–3.44) and LTFU (AHR, 1.36; 95% CI, 1.07–1.72) (Table, Supplemental Digital Content 3, http://links.lww.com/INF/B970). Similarly, compared with children with hemoglobin ≥8 g/dL, children with hemoglobin <8 g/dL had increased mortality (AHR, 1.42; 95% CI, 1.02–1.97) and LTFU (AHR, 1.30; 95% CI, 1.00–1.68).

Compared with HIV-1-infected children, HIV-2-infected and HIV-1 and HIV-2 reactive children had borderline increased mortality (AHR, 3.06; 95% CI, 0.96–9.73, $P = 0.059$), but not LTFU (Table, Supplemental Digital Content 3, http://links.lww.com/INF/B970).

Facility-level Predictors

Compared with children enrolled at larger facilities, children enrolled at smaller facilities had higher risk of LTFU (AHR, 1.86; 95% CI, 1.20–2.90), but not death (Table, Supplemental Digital Content 3, http://links.lww.com/INF/B970). Children enrolled at ART facilities reporting nurse dissatisfaction with working conditions had increased LTFU risk (AHR, 1.66; 95% CI, 1.10–2.50), but not mortality. Children enrolled at clinics providing integrated nutrition support had 34% lower LTFU risk (AHR, 0.66; 95% CI, 0.44–0.97), and borderline reduced mortality (AHR, 0.58; 95% CI, 0.31–1.09, $P = 0.089$).

DISCUSSION

This is the largest and first nationally representative pediatric ART outcome evaluation reported from Côte d'Ivoire.[7,8] The

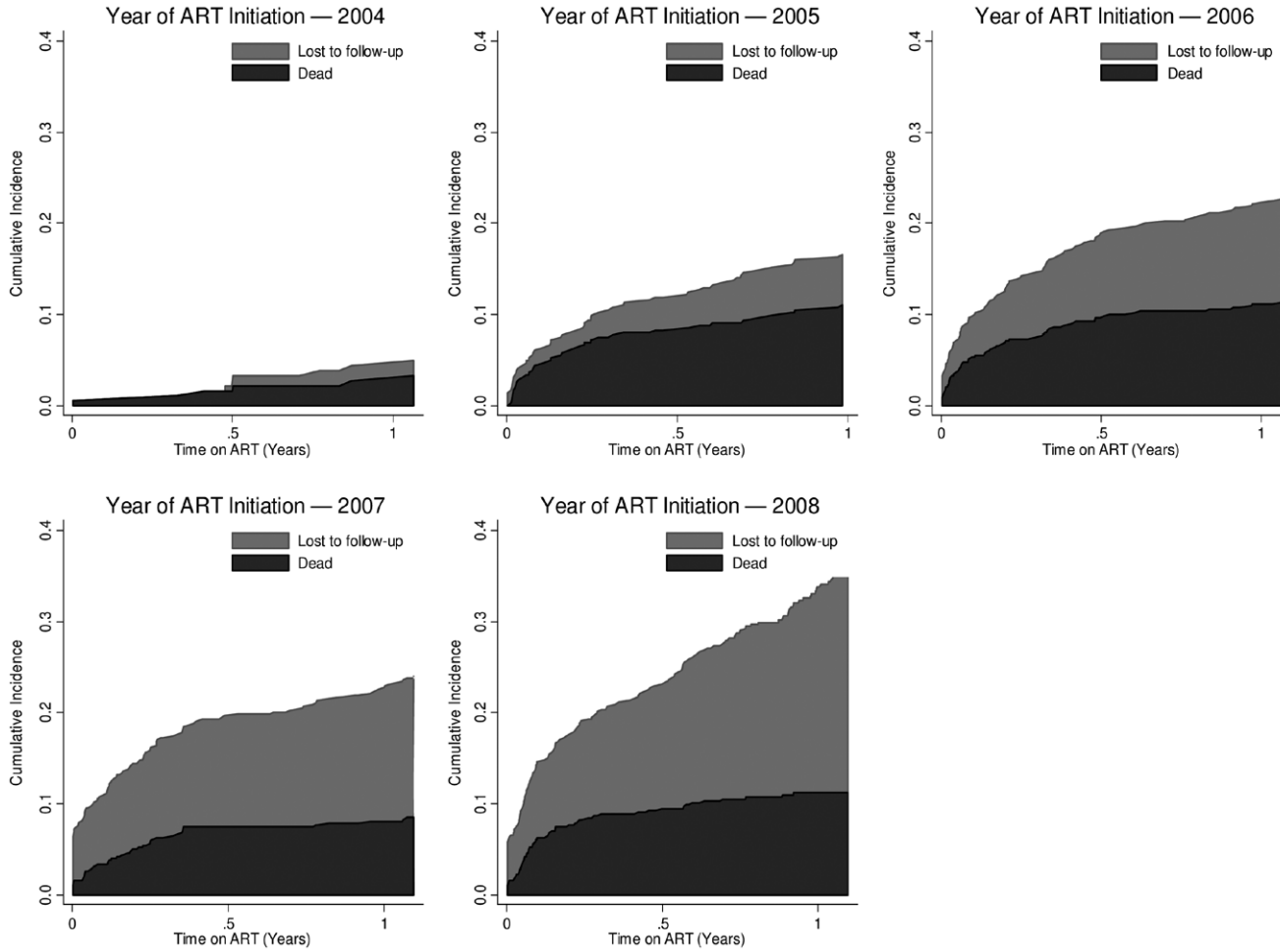

FIGURE 1. Incidence of death and loss to follow-up among Ivorian children initiating ART during 2004–2008.

report has important findings related to temporal trends in patient characteristics at ART initiation, trends in ART outcomes over time, and observed associations between facility-level characteristics and ART outcomes.

Trends in Patient Characteristics at ART Initiation Over Time

Disappointingly, only 21% of ART enrollees were <2 years at enrollment during 2004–2008, and this proportion did not increase significantly during 2004–2008. Randomized trials have shown that early postnatal diagnosis and immediate ART for perinatally HIV-infected children, rather than delayed ART, provides a survival benefit.[23,24] In Côte d'Ivoire, ongoing initiatives to expand access to ART for children <2 years include scale-up of early infant diagnosis services, ensuring availability of appropriate infant formulations, and training of personnel to provide ART for very young children.[4]

In addition to improving ART access for young children, increasing the availability of infant formulations and training of providers might improve outcomes of young ART enrollees. As in other evaluations,[25] ART enrollment at younger ages during 2004–2008 was independently predictive of death. This is largely because children starting ART before 2 years of age are more likely to have rapid disease progression, a challenge that is compounded if health providers have insufficient training or infant formulations are unavailable.[3,26,27]

Suboptimal regimens were prescribed to about 7% of all children and this did not improve over time. The most common suboptimal regimens prescribed were those containing efavirenz for children <3 years.[24] Notably, 17% of all children were prescribed unboosted nelfinavir. Although not considered suboptimal in this analysis, efavirenz is a better option for children ≥3 years, and lopinavir–ritonavir a better option for children <3 years.[28] High-dose requirements,[29,30] and lower potency compared with ritonavir-boosted agents, are disadvantages of nelfinavir.[10] Clinician training in prescription practices is ongoing.

Only 9% of ART enrollees had documented completion of recommended vaccines and this did not change significantly over time. Suboptimal vaccination completion among HIV-infected children has been reported in other countries.[31] Clinician hesitancy to provide live attenuated vaccines (measles and yellow fever vaccines) to symptomatic children might explain low rates of these 2 vaccines, however, all children should have received the DTPPH series in the first 8–12 months of life.[32] As absent documentation of routine vaccination completion was predictive of both mortality and LTFU, evaluating reasons for missing vaccination documentation, and implementing training and supervision efforts to ensure vaccination and its documentation is important. WHO recommends that HIV-infected children receive all vaccinations recommended for HIV-negative children, except the Bacillus Calmette–Guerin (BCG) vaccine, due to risk of disseminated BCG disease in immunocompromised children.[24,32]

Disappointingly, no significant reductions over time in markers of advanced HIV disease at ART initiation were observed, with prevalence of WHO stage III/IV, moderate to severe undernutrition (WAZ ≤−2), and severe anemia remaining constant and median CD4% remaining low (9–11%) during 2004–2008. As in other studies, these markers of advanced disease were predictive of mortality.[7,8,25,33] Programs aimed at accelerating access to early infant diagnosis, ensuring linkage of HIV-positive children to ART clinics, and adoption of new WHO guidelines that recommend ART initiation at age <5 years regardless of CD4%,[34] are potential strategies that could reduce the prevalence of advanced HIV disease among enrollees in the future.[28]

Trends in Patient Outcomes Over Time

Compared with 12-month attrition reported from other resource-limited countries (0–20% according to a recent meta-analysis),[33] our overall reported 12-month attrition (22%) is high. In addition, the annual increases in 12-month attrition, due to increases in both mortality and LTFU are concerning. Increasing rates of LTFU have been observed in African adult ART programs,[6,35,36] and among pediatric ART enrollees included in a recent multicountry cohort analysis from Africa and South East Asia.[37] Yearly increases in observed LTFU may be related to political instability that produced 2 civil wars during 2000–2010. Political instability has been shown to adversely affect clinic attendance and adherence in Kenya.[38] Alternatively, as the patient-to-provider ratios have increased, caregiver frustration with wait times and overcrowded facilities may have increased rates of default from care.[36,39–41] Similarly, increases in patient burden at central facilities and decentralization efforts may have increased the likelihood of undocumented transfers.[36] Further research to understand reasons for patient default from ART is needed to facilitate a programmatic response.

Increasing rates of mortality are more concerning and harder to explain. Expansion of the ART program to more rural areas of the country, where health status of children entering care may be lower, might have contributed to observed increases in mortality. Alternately, interruption of ART during political instability or increasing nonadherence to ART as a result of care-giver frustration with overcrowded facilities may account for increasing mortality.[38,42] Further research to explore causes of increasing mortality is needed.

Facility-level Predictors of Outcomes

Eleven of 29 facilities implemented a WHO-recommended HIV nutrition program,[11] involving regular growth assessment and food supplementation when indicated. Children attending these 11 facilities had lower risk of LTFU and borderline lower risk of death. Food supplementation for under-nourished ART enrollees may be especially important in Côte d'Ivoire,[43] which is ranked 170 of 187 on the human development index,[44] and where >50% of households with HIV-infected residents reported food insecurity in a recent survey.[45] To our knowledge, this is the first study showing benefit of a structured nutrition program for pediatric ART enrollees.[46] Scale-up of the integrated nutrition program to all pediatric ART facilities could improve outcomes.

Children attending clinics reporting nurse dissatisfaction with working conditions had higher LTFU rates. Nurse dissatisfaction may be correlated with patient dissatisfaction with clinic services, which has been associated with lower adherence and retention in HIV care.[47–50] Causes of nurse dissatisfaction are unknown but might include burnout,[51] or dissatisfaction with career advancement opportunities.[52] Implementing interventions to address nurse dissatisfaction could help to improve program outcomes.[53,54]

Similar to reports from adult ART programs in Abidjan,[19] initiating ART at smaller sites was associated with higher LTFU rates. Increased LTFU at smaller facilities could reflect lower quality services at peripheral clinics.[55,56] Alternately, inadequate documentation of ART follow-up or undocumented transfers between facilities may be more common at smaller facilities due to limited human resources, training or supervision.[57]

Limitations

Findings in this report are subject to several limitations. First, mortality estimates represent only documented mortality. A certain proportion of children observed to be LTFU will likely have died after defaulting care, so mortality is underestimated.[58] Second, missing data on patient characteristics at ART start likely introduced

nondifferential measurement error. Third, site-level characteristics were assessed at one point in time and the analysis does not account for changing facility characteristics over time. Fourth, while the study is representative of about 94% of children starting ART in Côte d'Ivoire during 2004–2008, it is not representative of children starting ART at very small facilities (≤10 pediatric ART enrollees by December 2008). Finally, as this is an observational study, the results may be affected by residual confounding.[26]

CONCLUSIONS

Children starting ART in 2008 were nearly 4-fold more likely to die and 8-fold more likely to be LTFU than enrollees in 2004. Causes for these changes are unknown and require further research. Earlier diagnosis and ART initiation, improved ART regimen choices for children <3 years, monitoring and ensuring age-appropriate vaccination completion, scale-up of integrated nutrition programs and addressing causes of nurse dissatisfaction with working conditions, should be prioritized for pediatric ART program improvement initiatives.

AUTHORS' CONTRIBUTIONS:

A.F.A., M.Z.T., K.A.E., J.S.K., V.E., R.W.S., J.E., E.D.R., G.A., R.M. and T.V.E. conceived and designed the study; A.F.A., M.Z.T., K.A.E., J.S.K., V.E., R.W.S., F.M., J.S., J.E., E.D.R., G.A., R.M. and T.V.E. supervised and implemented the study; A.F.A., R.W.S. and J.S. analyzed the data and A.F.A., M.Z.T., K.A.E., J.S.K., V.E., R.W.S., F.M., J.S., J.E., E.D.R., G.A., R.M. and T.V.E. wrote and reviewed the paper.

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