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Survival Benefit of Early Infant Antiretroviral Therapy is Compromised when Diagnosis is Delayed

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Abstract

Late presentation is common among African HIV-1-infected infants. Incidence and correlates of mortality were examined in 99 infants with HIV-1 diagnosis by age 5 months. Twelve-month survival was 66.8% (95% confidence interval, 55.9%, 75.6%). WHO stage 3/4, underweight, wasting, microcephaly, low hemoglobin, pneumonia, and gastroenteritis predicted mortality. Early HIV-1 diagnosis with ART before symptomatic disease is critical for infant survival.

Keywords

Pediatric; Infant; HIV-1; Antiretroviral therapy; Mortality

Many African HIV-1 infected children present late for HIV care, and often at hospitalization.¹⁻³ This late presentation is likely to undermine the benefits of early antiretroviral therapy (ART) their survival. The Children with HIV Early Antiretroviral Therapy (CHER) study from South Africa demonstrated that empiric ART provided within the first 6-12 weeks of life resulted in 96% survival at 12 months.⁴ However, children enrolled in CHER were asymptomatic with baseline CD4% ≥ 25%. While encouraging, the inclusion criteria for CHER may limit generalizability to children who present later for medical care. Here, we determined incidence and correlates of mortality among HIV-1-infected infants diagnosed at up to 5 months of age and followed for at least 12 months following ART.

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METHODS

Study Population

Ethical approval was obtained from the University of Washington and the Kenyatta National Hospital Institutional Review Boards. From 2007-2009, HIV-1-infected infants were enrolled into a randomized clinical trial (Optimizing Pediatric HAART 03 [OPH03]) with a 2-year pre-randomization phase (NCT00428116). In Nairobi, HIV-1-infected infants were identified after routine infant HIV-1 DNA PCR testing offered at prevention of mother to child transmission (PMTCT) clinics and hospital wards. Inclusion criteria were: 1) confirmed HIV-1 DNA positive, 2) no previous ART (except for antiretroviral drugs used for PMTCT), 3) caregiver planned to reside in Nairobi for 3 years, 4) age <4.5 months. Before 2009, children with suspected active tuberculosis (TB) were excluded.

At enrollment, participants received a physical examination, caregivers provided demographic information, and infants and biological mothers provided blood specimens. A follow-up visit was scheduled for ART initiation. Infants identified through hospital-based testing generally initiated ART following stabilization and discharge, per standard protocol, although in some instances, these infants initiated ART while in hospital. ART regimens generally included zidovudine (ZDV), lamivudine, and either nevirapine (NVP) or lopinavir-boosted-ritonavir, for infants with prior NVP exposure. 99% of infants received trimethoprim-sulfamethoxazole (cotrimoxazole) prophylaxis before or at enrollment. Participants attended monthly clinic visits following ART. Likely causes of death were abstracted from hospital medical records or ascertained by verbal autopsy. CD4 percents and counts were obtained using flow cytometry.

Statistical Analysis

Z-scores for growth parameters were calculated using the WHO child growth standards.⁵ Underweight, stunting, wasting, and microcephaly were defined as weight-for-age (WAZ), height-for-age (HAZ), weight-for-height (WHZ), and head circumference (HCZ) Z-score < -2. Anemia was defined as hemoglobin <8 g/dl.¹ Probability of survival was estimated using Kaplan-Meier survival analysis and univariate and multivariate Cox proportional hazards models were used to determine correlates of mortality. Survival was evaluated using time from enrollment for analyses including all infants and time from ART initiation for analyses restricted to infants initiating ART. Collinearity between cofactors was evaluated and multivariate models are presented for non-collinear cofactors. Analyses were performed using Stata IC 10.1 (College Station, Texas).

RESULTS

Cohort characteristics

Ninety-nine HIV-1-infected infants were enrolled at ages 1-5 months (median, 3.7 months; Table 1). At baseline, most infants were underweight (57.6%), stunted (49.5%), or wasted (30.3%). Ten (12.8%) infants had not been breastfed. Slightly over half (54%) had received PMTCT. Infants were severely immunosuppressed; the median CD4% was 18%, 47 (49.0%) infants were diagnosed with WHO Stage 3/4 disease, and 59 (59.6%) had been hospitalized. None had clinical signs of pulmonary or extrapulmonary TB.

Infant follow-up

Infants were followed for a median of 16.1 months (interquartile range [IQR], 1.2, 27.6) pre-randomization, for a total of 123.1 person-years. Overall, there were 29 (29.3%) deaths, 10 (10.1%) losses to follow-up (LTFU), and 6 (6.1%) withdrawals, of which 12 deaths, 3

LTFU, and 4 withdrawals occurred pre-ART. Eighty (80.8%) infants initiated ART at a median 14 days from enrollment (IQR, 7, 21).

Infant survival

Overall, the 12-month probability of survival was 66.8% (95% CI, 55.9%, 75.6%). Of those who died, 12 (41.4%) had not yet initiated ART (median time to death, 11 days [IQR, 5, 27]). The overall rate of death was 23.6 (95% CI, 16.4, 33.9) per 100 person-years with decreasing rates from 119.6 per 100 person-years (22 events during 18.4 person-years; 95% CI, 78.7, 181.6) during months 0-3, 39.5 per 100 person-years (95% CI, 17.7, 87.9) in months 4-6, and 3.2 per 100 person-years (95% CI, 0.46, 23.0) during months 7-24. Among the 80 infants who initiated ART, 12-month survival was 77.4% (95% CI, 66.2%, 85.3%), with an overall rate of death of 14.3 (95% CI, 8.9, 23.0) per 100 person-years.

Correlates of infant mortality

Among all infants, significant baseline correlates of mortality included younger age (hazard ratio [HR]=0.66), baseline CD4% <10% (HR=5.94), baseline WHO stage 3/4 (HR=4.05), underweight (HR=3.28), wasting (HR=5.60), microcephaly (HR=2.71), hemoglobin <8 g/dL (HR=3.44), pneumonia (HR=2.31) and gastroenteritis (HR=4.73) (Table 1). In a multivariate model, baseline WHO stage 3/4 (adjusted HR [aHR]=4.07) and hemoglobin <8 g/dL (aHR=4.63) remained significant cofactors of mortality.

In analyses restricted to infants who initiated ART, significant correlates of mortality were generally similar to those for the overall cohort; although microcephaly and gastroenteritis were no longer associated with mortality in this subset. Plasma HIV-1 RNA level (HR=2.52) was associated with mortality for infants initiating ART but not the overall cohort.

Discussion

This study demonstrated substantial mortality in infants with acute HIV-1 infection who received HIV care by age 5 months. Twelve-month survival among the cohort was 66.8%. Younger age, WHO stage 3/4, underweight, wasting, microcephaly, low hemoglobin, presence of pneumonia, and presence of gastroenteritis predicted mortality.

Among infants who did not start ART and died, median time to death was 11 days, suggesting a very short window of opportunity to provide ART in HIV-1-infected infants. The median time from enrollment to ART was 14 days. Standard adherence counseling sessions took 1-2 weeks and hospitalized infants were stabilized and discharged prior to ART, suggesting streamlined adherence counseling and emergent ART for hospitalized infants warrant consideration.

Consistent with previous studies of older children with chronic HIV-1,^{1, 3, 6-9} HIV-1 disease severity, poor growth, low hemoglobin, pneumonia, and gastroenteritis were all associated with mortality, and may reflect the contribution of these factors towards delay of ART or may reflect irreversible HIV-1 disease. Gastroenteritis and microcephaly correlated with mortality for the overall cohort, but not for infants who initiated ART, implying these cofactors are linked to particularly rapid disease course.

In combination, pneumonia and gastroenteritis contributed to approximately two-thirds of mortalities (see Table, Supplemental Digital Content 1, <http://links.lww.com/INF/B187>, listing causes of death). In addition, there was overlap between these diagnoses at enrollment and at death: 2/8 (25%) subjects who died of gastroenteritis had gastroenteritis at enrollment, and 5/9 (54%) subjects who died of pneumonia had pneumonia at enrollment.

Our results highlight a need for rapid management strategies for pneumonia and gastroenteritis in HIV-1 infected children.

Slightly over half (54%) of OPH03 infants had access to PMTCT, but in general, still lacked early infant diagnosis (by age 6 weeks). We found substantially higher mortality than did the South African CHER trial (10 deaths per 100 person-years), which enrolled infants with HIV-1 diagnosis at age <3 months (median, 1.7 months), and randomized to immediate vs deferred ART.⁴ The 12-month survival was significantly higher in CHER than in our study (92% vs. 71%; $P < 0.0001$). CHER infants had higher baseline CD4 percents (35% vs. 18%) and WAZ (-0.7 vs. -2.6). These differences are likely due to rapid clinical course in HIV-1-infected infants,¹⁰ and further reflect the survival benefit of early infant HIV-1 diagnosis and treatment.

For context, we compared overall survival in OPH03 vs. HIV-1-infected untreated infants born from 1999-2002 (CTL cohort) and surviving to age 4 months.¹⁰ Mortality was lower overall in OPH03 than in untreated infants (24 vs. 48 per 100 person-years) ($P = 0.07$) (see Figure, Supplemental Digital Content 2, <http://links.lww.com/INF/B188>, depicting survival by cohort). Still, improved survival in OPH03 infants vs. historical untreated infants was not apparent until over 6 months after HIV-1 diagnosis. This lag suggests infants with symptomatic HIV-1-disease may not be salvageable and/or the full impact of ART in symptomatic infants may not be immediate.

The main strength of this study is inclusion of infants with advanced HIV-1 disease and late HIV-1 diagnosis, both typical in Africa.¹⁻³ Our comparisons between cohorts are limited by demographic and regional differences. Differences in PMTCT coverage (higher for both CHER and CTL than for OPH03), and type (majority with single-dose-NVP alone for CHER and OPH03 and majority with ZDV alone for CTL¹⁰) may have influenced subsequent disease progression. Many OPH03 infants were identified at hospital, limiting comparability with CTL and CHER, which were identified through PMTCT. Although retention was similar in CTL (89%) and in OPH03 (90%), retention was higher in CHER (96%), and it is possible that the mortality difference between CHER and OPH03 was underestimated if infants who were lost to follow-up actually died.

Our study underscores the importance of early identification and prompt treatment of HIV-1-infected infants by age 6 weeks. For infants diagnosed later, it will remain important to discern whether accelerated ART improves survival. Early access to HIV-1 diagnosis and treatment, prior to onset of symptoms, will remain the key intervention for survival among HIV-1-infected infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1
Summary of baseline characteristics and univariate analyses of correlates of mortality

Correlate	All Infants (N=99) ^K			Infants who initiated ART (N=80) ^L		
	n (%) or Median (IQR)	HR (95% CI) [*]	P	n (%) or Median (IQR)	HR (95% CI) [*]	P
Age (months)	3.7 (2.9, 4.0)	0.66 (0.44, 0.99)	0.043	3.7 (2.9, 4.0)	0.59 (0.35, 1.0)	0.048
Male	50 (50.5%)	1.62 (0.77, 3.40)	0.2	37 (46.3%)	1.05 (0.41, 2.73)	0.9
Weight at birth	3.0 (2.7, 3.4)	1.10 (0.59, 2.05)	0.8	3.0 (2.7, 3.4)	1.15 (0.51, 2.60)	0.7
Received to PMTCT	50 (53.8%)	0.96 (0.46, 2.03)	0.9	39 (52.0%)	0.65 (0.24, 1.75)	0.4
<i>HIV-1 disease status</i>						
Plasma HIV-1 RNA log ₁₀ copies/mL	6.55 (5.99, 7.08)	1.24 (0.75, 2.06)	0.4	6.59 (5.98, 7.21)	2.52 (1.06, 5.98)	0.037
WHO stage 3 or 4	47 (49.0%)	4.05 (1.73, 9.49) ^J	0.001	34 (43.6%)	3.39 (1.19, 9.62)	0.022
CD4 percentage	18 (14, 24)	0.95 (0.90, 1.00)	0.063	18 (14, 24)	0.96 (0.90, 1.03)	0.2
CD4 percentage <10	10 (10.4%)	4.94 (2.07, 11.78)	<0.001	7 (8.8%)	4.92 (1.60, 15.17)	0.006
CD4 count (cells/ μ L)	1,302 (755, 1,953)	0.96 (0.91, 1.02) ^A	0.2	1,302 (766, 1,908)	0.94 (0.87, 1.01) ^A	0.095
<i>Growth</i>						
Underweight (WAZ < -2)	57 (57.6%)	3.28 (1.33, 8.07)	0.01	44 (55.0%)	2.25 (0.79, 6.38)	0.13
Stunted (HAZ < -2)	49 (49.5%)	1.73 (0.82, 3.67)	0.15	40 (50.0%)	1.58 (0.60, 4.14)	0.4
Wasted (WHZ < -2)	30 (30.3%)	5.60 (2.63, 11.91)	<0.001	19 (23.8%)	4.59 (1.76, 11.91)	0.002
Microcephalic (HCZ < -2)	18 (18.2%)	2.71 (1.23, 5.98)	0.013	11 (13.8%)	1.40 (0.40, 4.89)	0.6
<i>Morbidity</i>						
Hemoglobin <8 g/dL	13 (13.5%)	3.44 (1.45, 8.19) ^J	0.005	9 (11.3%)	3.36 (1.09, 10.34)	0.035
Hospitalized since birth	59 (59.6%)	2.22 (0.98, 5.01)	0.055	44 (55.0%)	1.61 (0.60, 4.36)	0.3
Fever	8 (8.4%)	1.14 (0.34, 3.77)	0.8	6 (7.8%)	0.63 (0.08, 4.78)	0.7
Upper respiratory tract infection	9 (9.1%)	0.60 (0.14, 2.52)	0.5	8 (10.0%)	0.52 (0.07, 3.90)	0.5
Pneumonia	31 (31.3%)	2.31 (1.11, 4.78)	0.025	22 (27.5%)	2.40 (0.93, 6.23)	0.07
Gastroenteritis	8 (8.2%)	4.73 (1.91, 11.74)	0.001	3 (3.8%)	1.33 (0.17, 10.04)	0.8

* Per unit increase for all continuous variables except where indicated.

^A Per 100 cells/ μ L increase.

^J Results were similar in a multivariate model including WHO Stage 3/4 (HR, 4.07, 95% CI, 1.71, 9.71; p = 0.002) and hemoglobin <8g/dL (HR, 4.63, 95% CI, 1.45, 8.19; p = 0.001).

[§]NA, not applicable. Cox proportional hazards model did not converge.

[¶]Birthweight, N=94; Exposed to PMTCT, N= 93; Plasma HIV-1-RNA, N=81; WHO stage, N=96; CD4 percent and count, N=96; Hemoglobin, N=96; Fever, N=95; Gastroenteritis, N=98.

[‡]Birthweight, N=76; Exposed to PMTCT, N= 75; Plasma HIV-1-RNA, N=65; WHO stage, N=78; Fever, N=77.