Mortality in Children with Human Immunodeficiency Virus Initiating Treatment: A Six-Cohort Study in Latin America

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Objectives To assess the risks of and factors associated with mortality, loss to follow-up, and changing regimens after children with HIV infected perinatally initiate combination antiretroviral therapy (cART) in Latin America and the Caribbean.

Study design This 1997-2013 retrospective cohort study included 1174 antiretroviral therapy–naïve, perinatally infected children who started cART age when they were younger than 18 years of age (median 4.7 years; IQR 1.7-8.8) at 1 of 6 cohorts from Argentina, Brazil, Haiti, and Honduras, within the Caribbean, Central and South America Network for HIV Epidemiology. Median follow-up was 5.6 years (IQR 2.3-9.3). Study outcomes were all-cause mortality, loss to follow-up, and major changes in cART. We used Cox proportional hazards models stratified by site to examine the association between predictors and times to death or changing regimens.

Results Only 52% started cART at younger than 5 years of age; 19% began a protease inhibitor. At cART initiation, median CD4 count was 472 cells/mm^3 (IQR 201-902); median CD4% was 16% (IQR 10-23). Probability of death was high in the first year of cART: 0.06 (95% CI 0.04-0.07). Five years after cART initiation, the cumulative mortality incidence was 0.12 (95% CI 0.10-0.14). Cumulative incidences for loss to follow-up and regimen change after 5 years were 0.16 (95% 0.14-0.18) and 0.30 (95% 0.26-0.34), respectively. Younger children had the greatest risk of mortality, whereas older children had the greatest risk of being lost to follow-up or changing regimens.

Conclusions Innovative clinical and community approaches are needed for quality improvement in the pediatric care of HIV in the Americas. *(J Pediatr 2017;182:245-52).*

The use of combination antiretroviral therapy (cART) has been effective in reducing mortality markedly among children and adolescents infected with HIV[1-3]; however, in the US, mortality rates among children with HIV still are approximately 30 times greater than the general pediatric population.[4] Deaths due to opportunistic infections have declined in the cART era but are still seen in resource-limited settings; non–AIDS-defining infections and multiorgan failure remain major causes of mortality in children with HIV.[4] Studies performed in the US, Europe, and South Africa suggest that most deaths occur in the first 6 months following antiretroviral therapy (ART) initiation, perhaps reflecting therapy that comes too late for effective immune reconstitution.[5] Mortality trends in the US Perinatal AIDS Collaborative Transmission Study demonstrated that birth year, percentage of CD4+ T lymphocytes (CD4 percent), anthropometric measures, timing of HIV transmission, and maternal US Centers for Disease Control and Prevention AIDS classification were independent predictors of mortality.[6] At cART initiation, lower CD4 percent, an AIDS-defining diagnosis, younger age, and belonging to an earlier birth cohort have been associated with an increased risk of death.[4]

Post-cART mortality rates remain greater in resource-limited settings compared with rates in developed settings; children in these settings begin cART at greater viral loads and lower CD4 levels.[7] The HIV epidemic in Latin America and the Caribbean has remained mostly stable during the past decade, with slowly declining HIV incidence and AIDS-related deaths resulting in a slightly

ART	Antiretroviral therapy
cART	Combination antiretroviral therapy
CCASAnet	Caribbean, Central and South America network
CD4 count	Absolute CD4+ T lymphocyte count
CD4 percent	Percentage of CD4+ T lymphocytes
HR	Hazard ratio
LTFU	Lost to follow-up
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission

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increased estimated number of persons living with HIV, from 1.60 million in 2000 to 1.75 million in 2012, of whom 56 000 are children.[8] Rates of mortality after initiating cART have been studied for Latin American adults,[9,10] but no study has yet characterized mortality rates among children starting cART in multiple cohorts in the region. We sought to estimate rates of mortality for children during the first year and beyond on cART and to assess predictors of mortality and determinants of initial regimen change among children in the Caribbean and Central and South America.

Methods

The Caribbean, Central and South America Network for HIV Epidemiology (CCASAnet) has been described elsewhere.[11] To summarize, CCASAnet is a consortium of HIV clinics in Latin America and Haiti, 1 of 7 global regions affiliated with the International Epidemiologic Databases to Evaluate AIDS network supported by the US National Institutes of Health. Six clinics providing pediatric care contributed data to this study: Hospital Fernandez, Buenos Aires, Argentina; Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; Universidade Federal de São Paulo, São Paulo, Brazil; Le Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes, Port-au-Prince, Haiti; and Hospital Escuela Universitario and Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras. Deidentified data were sent to the CCASAnet Data Coordinating Center at Vanderbilt University, Nashville, Tennessee, for data harmonization, quality checks, and analysis. The CCASAnet Data Coordinating Center at Vanderbilt University checked data for internal consistency. Institutional ethics review boards at each of the study sites and Vanderbilt University approved this study and waived the need for informed consent.

The study included ART-naïve, children with HIV who were infected perinatally and started cART when they were younger than 18 years of age, after clinic enrollment, and between 1997 and 2013. ART exposure as part of prevention of mother-to-child transmission (PMTCT) programs was not considered ART. Patients whose mode of infection was missing or unknown but who were diagnosed with HIV by the age of 10 years also were included. Most children were referred in by other clinics when HIV diagnosis was suspected/established. On average, less than one-quarter of children were enrolled in clinic who were younger than 1 year of age.

In this analysis, patients were followed from the date of cART initiation (baseline) to death or last visit. Children were considered lost to follow-up (LTFU) when their most recent visit was more than 12 months before the cohort database closing date, determined by the most recent visit in the cohort database. Absolute CD4+ T lymphocyte count (CD4 count) and CD4 percent at cART initiation were defined by the use of the measurements closest to cART initiation within a window of 180 days before and 7 days after. For those sites that routinely measure plasma HIV-1 RNA, the closest measurement to the date of cART initiation within a window of 180 days before and 0 days after was chosen. Clinical stage before cART initiation of was categorized as AIDS or not AIDS; clinical AIDS was defined as US Centers for Disease Control and Prevention stage C, World Health Organization stage IV, or a specification of an AIDS diagnosis at the child's first visit.

Study outcomes were all-cause mortality, LTFU, and change of cART regimen. cART was defined as protease inhibitor (PI)-based (1 ritonavir-boosted or unboosted PI plus 2 nucleoside reverse transcriptase inhibitors [NRTI]), non-nucleoside reverse transcriptase inhibitor (NNRTI)-based (1 NNRTI plus 2 NRTIs), or other combinations (including triple NRTI regimens and all other regimens containing at least 3 drugs). A regimen change was defined as a single drug change outside of the regimen class, a switch of 2 or more antiretrovirals in the initial cART regimen, or the addition of 2 or more antiretrovirals from the initial cART regimen. A regimen change also included deleting 1 or more antiretrovirals from the initial cART regimen so that the new regimen no longer met the definition of cART.

The cumulative incidence of death was estimated via the use of Kaplan-Meier methods. The cumulative incidences of regimen change and LTFU were estimated treating death as a competing event. Cox proportional hazards models were stratified by site and used to examine with cause-specific hazard ratios (HRs) the association between predictors and the times to death, LTFU, or changing regimens. Predictors of interest that were included in the models were age, sex, CD4 count at cART initiation (square root transformed), year of cART initiation, first cART regimen class (including a PI, or not including a PI), and clinical AIDS. Continuous predictors were included in the models by the use of restricted cubic splines with predictors expanded by the use of 4 knots placed at default locations (5th, 35th, 65th, and 95th quantiles). HRs for continuous variables were presented by comparing the predicted hazards at specific prespecified levels vs reference levels (eg, CD4 = 200 cells/mm^3 vs CD4 = 350 cells/mm^3). Missing CD4 counts (n = 118; 10% of patients) were multiply imputed 10 times using the R function *aregImpute*, which uses additive regression, bootstrapping, and predictive mean matching,[12] and then incorporated into analyses via a standard multiple imputation techniques.[13] To verify the fit of our imputation models, in the subset of patients with nonmissing CD4 count, we compared the mean difference between imputed CD4 (pretending CD4 was unavailable) and observed CD4; the mean difference for the 10 imputation replications varied from −40 to 37 cells/mm^3, which represent −0.06 to 0.06 SDs from zero, suggesting the imputation was adequate. CD4 percent is the preferred measure of disease progression in subjects younger than 5 years of age rather than CD4 count; however, not all sites recorded this information. Therefore, secondary analyses were performed for children younger than 5 in the subset of sites that recorded CD4 percent.

All analyses were performed with R statistical software (The R Project for Statistical Computing, Vienna, Austria). Analysis code is posted at http://biostat.mc.vanderbilt.edu/ArchivedAnalyses.