Published in final edited form as:

J Pediatr. 2017 March ; 182: 245–252.e1. doi:10.1016/j.jpeds.2016.12.034.

Mortality in children with human immunodeficiency virus initiating treatment: A six-cohort study in Latin America

Marco T. Luque, MD¹, Cathy A. Jenkins, MS², Bryan E. Shepherd, PhD², Denis Padgett, MD¹, Vanessa Rouzier, MD³, Regina Célia M. Succi, MD⁴, Daisy M. Machado, MD⁴, Catherine C. McGowan, MD², Sten H. Vermund, MD, PhD², and Jorge A. Pinto, MD, DSc⁶

¹Departamento de Pediatría, Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras

²Departments of Biostatistics, Medicine, and Pediatrics, Vanderbilt University School of Medicine, and Vanderbilt Institute for Global Health, Nashville, Tennessee, USA

³Le Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes, Port-au-Prince, Haiti

⁴Department of Pediatrics, Escola Paulista de Medicina, Universidade Federal de São Paulo/UNIFESP, São Paulo, Brasil

⁶Department of Pediatrics, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil

Abstract

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

Study design—This 1997–2013 retrospective cohort study included 1174 ART-naïve perinatally-infected children who started cART age<18 years (median 4.7 years; interquartile range [IQR] 1.7–8.8) at one of six cohorts from Argentina, Brazil, Haiti, and Honduras, within the Caribbean, Central and South America Network for HIV Epidemiology (CCASAnet). Median follow-up was 5.6 years (interquartile range [IQR] 2.3 to 9.3). Study outcomes were all-cause mortality, loss to followup, and major changes/interruption/stopping of 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 <5 years of age; 19% began a protease inhibitor. At cART initiation, median CD4 count was 472 cells/mm³ (IQR: 201–902); median CD4% was 16% (IQR: 10–23). Probability of death was high in the first year of cART: 0.06 (95% confidence interval [CI]

Corresponding author: Jorge A. Pinto, MD, DSc, Department of Pediatrics, Faculdade de Medicina, Universidade Federal de Minas Gerais. Av. Alfredo Balena 190, room # 161, Belo Horizonte, MG, 30130-100, Brasil. Telephone: (55 31) 3409 9822, Fax: (55 31) 3273 0422, jpinto@medicina.ufmg.br.

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The authors declare no conflicts of interest.

0.04–0.07). Five years after cART initiation, the cumulative mortality incidence was 0.12 (CI 0.10–0.14). Cumulative incidences for loss to followup and regimen change after five years were 0.16 (CI 0.14–0.18) and 0.30 (CI 0.26–0.34), respectively. Younger children had the highest risk of mortality, whereas older children had the highest risk of being lost to followup or changing regimens.

Conclusions—Innovative clinical and community approaches are needed for quality improvement for HIV pediatric care in the Americas.

Keywords

HIV/AIDS; infectious diseases

The use of combination antiretroviral therapy (cART) has been effective in reducing mortality markedly among children and adolescents infected with HIV.^{1, 2, 3} However, in the United States (US) mortality rates among HIV-infected children are still approximately 30 times higher 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 multi-organ failure remain major causes of mortality in HIV-infected children.⁴ Studies performed in the US, Europe and South Africa suggest that most deaths occur in the first 6 months following 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 U.S. Centers for Disease Control and Prevention (CDC) 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 higher in resource-limited settings compared with rates in developed settings; children in these settings begin cART at higher viral loads and lower CD4 levels.⁷ The HIV epidemic in Latin America and the Caribbean has remained mostly stable over the past decade, with slowly declining HIV incidence and AIDS-related deaths resulting in a slightly increased estimated number of persons living with HIV (PLHIV), 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, Central and South America.

Methods

The Caribbean, Central and South America Network for HIV Epidemiology (CCASAnet) has been described elsewhere.¹¹ Briefly, CCASAnet is a consortium of HIV clinics in Latin America and Haiti, one of seven global regions affiliated with the International Epidemiologic Databases to Evaluate AIDS (IeDEA) network supported by the US National

Institutes of Health. Six clinics providing pediatric care contributed data to this study: Hospital Fernandez, Buenos Aires, Argentina (HF-Argentina); Universidade Federal de Minas Gerais, Belo Horizonte, Brazil (UFMG-Brazil); Universidade Federal de São Paulo, São Paulo, Brazil (UNIFESP-Brazil); Le Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes, Port-au-Prince, Haiti (GHESKIO-Haiti); Hospital Escuela Universitario and Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras (HE-Honduras and IHSS-Honduras). Deidentified data were sent to the CCASAnet Data Coordinating Center at Vanderbilt University, Nashville, TN, USA (VDCC), for data harmonization, quality checks, and analysis. The VDCC 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 HIV-infected children who were infected perinatally and started cART under the age 18 years, 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 were also included. Most children were referred in by other clinics when HIV diagnosis was suspected/established. On average, less than a quarter of children were enrolled in clinic with less than one 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 prior to 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 using 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 prior to cART initiation of was categorized as AIDS or not AIDS; clinical AIDS was defined as CDC stage C, World Health Organization (WHO) stage IV, or a specification of an AIDS diagnosis at the child's first visit.

Study outcomes were all-cause mortality, LTFU, and change in, interruption of, or stopping of cART regimen. cART was defined as protease inhibitor (PI)-based (one ritonavir-boosted or unboosted PI plus two nucleoside reverse transcriptase inhibitors [NRTI]), non-nucleoside reverse transcriptase inhibitor (NNRTI)-based (one NNRTI plus two NRTIs), or other combinations (including triple NRTI regimens and all other regimens containing at least three drugs). A regimen change was defined as a single drug change outside of the regimen class, a switch of 2 antiretrovirals in the initial cART regimen, or the addition of 2 antiretrovirals from the initial cART regimen. A regimen change also included a treatment interruption, defined as stopping all antiretrovirals for at least 10 days or deleting 1 antiretroviral from the initial cART regimen so that the new regimen no longer met the definition of cART.

The cumulative incidence of death was estimated using 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 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 protease inhibitor [PI], or not including a PI), and clinical AIDS. Continuous predictors were included in the models using restricted cubic splines with predictors expanded using 4 knots placed at default locations (5th, 35th, 65th, and 95th quantiles). Hazard ratios for continuous variables were presented by comparing the predicted hazards at specific pre-specified levels versus reference levels (e.g., CD4=200 cells/mm³ vs. CD4=350 cells/mm³). 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 using standard multiple imputation techniques.¹³ To verify the fit of our imputation models, in the subset of patients with non-missing 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/mm³, which represent -0.06 to 0.06 standard deviations from zero, suggesting the imputation was adequate. CD4 percent is the preferred measure of disease progression in subjects <5 years of age rather than CD4 count; however, not all sites recorded this information. Therefore, secondary analyses were performed for children <5 in the subset of sites that recorded CD4 percent.

All analyses were performed using R statistical software. Analysis code is posted at <http://biostat.mc.vanderbilt.edu/ArchivedAnalyses>.

Results

A total of 1174 children met inclusion criteria. The subjects included 17 (1.4%) from HF-Argentina, 255 (21.7%) from UFMG-Brazil, 84 (7.2%) from UNIFESP-Brazil, 615 (52.4%) from GHESKIO-Haiti, 190 (16.2%) from HE-Honduras, and 13 (1.1%) from IHSS-Honduras.

Table I shows characteristics of children starting cART by site. Approximately half of the children (614; 52.3%) started cART under the age of 5 years; the median (interquartile range [IQR]) age for cART initiation was 4.7 (1.7–8.8). The median age at HIV diagnosis was 3.3 years (IQR: 1.0–7.0); date of HIV diagnosis was missing for 26 (2%) children. More than half (53%) were female and the median year of cART initiation was 2005 (IQR: 2003–2009; range 1997–2013). Median age at cART initiation tended to increase with calendar year up until 2007–2008 after which it decreased, although patterns varied by site (Figure 3; available at www.jpeds.com). Time from enrollment to cART initiation varied substantially by site, but the overall median was 3.4 months (IQR: 1.1–14.1). At cART initiation, 36% of children had clinical AIDS, 60% did not, and 4% had an unknown clinical AIDS status. The median CD4 count at cART initiation was 472 cells/mm³ (IQR: 201–902); for children ≥5 years, the median CD4 count was 294 (IQR 114 to 494). For children <5, the median CD4 percent at cART initiation was 19% (IQR 13 to 28) in the subset for whom CD4 percent was available (60%). A PI-based regimen was initiated for 19% of children (29% of children <5

years and 8% if ≥ 5 years), although $>50\%$ initiated PI-based regimens at the sites in Argentina and Brazil whereas $<10\%$ initiated PI-based regimens at the sites in Haiti and Honduras. Lopinavir/ritonavir ($n=59$) and nelfinavir ($n=41$) were the most common PIs used.

Median follow-up was 5.6 years (IQR 2.3 to 9.3); follow-up was similar across age groups (e.g., median of 5.8 and 5.4 years for those <5 and ≥ 5 years at cART initiation, respectively). Twelve percent ($n=138$) of patients died during follow-up and 21% were LTFU.

The cumulative incidence of death and LTFU after cART initiation are shown in left and middle panels of Figure 1, respectively. The probability of death was high, 0.06 (95% confidence interval [CI] 0.04–0.07), in the first year of cART. The cumulative incidence of mortality five years after cART initiation was 0.12 (95% CI 0.10–0.14). The cumulative incidence of LTFU at 1 and 5 years was 0.06 (95% CI 0.04–0.07) and 0.16 (95% CI 0.14–0.18), respectively.

Table II shows the associations between patient characteristics at cART initiation and mortality, stratified by study site and adjusting for all other variables. Age was a strong predictor of mortality across the entire cohort ($p<0.001$) with younger children starting ART generally having a higher risk of mortality than older children. For example, after controlling for sex, CD4 count, year of first cART, first cART regimen class, clinical status, and study site, a child who initiated cART at the age of 6 months had an estimated hazard of death that was 2.6 times higher than that of a child starting at the age of 5 years (95% CI 1.6–4.2). However, there was some weaker evidence suggesting that the risk of mortality was also higher for adolescents (e.g., p -value for non-linearity was 0.001; adjusted HR comparing age 15 years with age 5 years was 1.33, 95% CI 0.74–2.41). The left panel of Figure 2 shows the predicted 5-year probability of mortality as a function of age, holding all other factors constant.

Baseline CD4 count was also a strong predictor of mortality, with those having lower CD4 counts at cART initiation having higher hazards of death. Similarly, children with a clinical AIDS diagnosis at baseline had almost twice the hazard of death as those who did not (hazards ratio [HR]=1.9, 95% CI 1.3–2.7). Year of cART initiation was not a strong predictor of mortality after controlling for other variables. Results were similar when the analysis was restricted to those sites that collected CD4 percent. Among children <5 years at cART initiation, those with CD4 percent of 10 had a hazard of mortality 1.75 times higher than those with CD4 percent of 25 (95% CI, 1.1–2.7).

Table II also shows the associations between patient characteristics at cART initiation and being LTFU, stratified by site and controlling for all other variables. Age was the strongest predictor of LTFU ($p<0.001$). For example, after adjusting for other variables, the hazard of being LTFU was 2.23 times higher for children 15 years old than for children 5 years old. The estimated probability of being LTFU as a function of age is shown in middle panel of Figure 2.

A total of 370 children (32%) changed regimens during follow-up; 28 removed one or more antiretroviral and the remaining 342 switched/added ≥ 2 drugs and/or made a single out-of-

class drug substitution. Of the 370 children who changed regimens, 198 (54%) had failure/non-adherence listed as the reported reason for change (treatment failure [111], virologic failure [57], non-adherence [20], drug resistance based on HIV genotype [8], immunologic failure [1], and clinical progression [1]). Toxicity was the reported reason for change for 49 (13%) patients with abdomen/gastrointestinal toxicities being the most common (n=14). Other reported reasons for changing regimens included TB treatment drug interaction (n=20), drugs not available (n=16), more effective or simplified treatment available (n=11), unspecified patient or physician decisions (n=16), or unspecified other reasons (n=24). Reason for changing regimen was unknown for 36 (10%) patients. The most common regimens changed were lamivudine+zidovudine+efavirenz (n=98), didanosine+zidovudine+nelfinavir (n=51), lamivudine+zidovudine+nevirapine (n=34), didanosine+zidovudine+efavirenz (n=33), and lamivudine+zidovudine+nelfinavir (n=30).

The right panel of Figure 1 illustrates the cumulative incidence of regimen change with death treated as a competing risk. The 1- and 5-year incidences of regimen change were 0.08 (95% CI 0.06–0.09) and 0.29 (95% CI 0.26–0.32), respectively. Table II shows the associations between patient characteristics at cART initiation and regimen change, stratified by study site and controlling for all other variables. Older age at cART initiation was associated with a higher hazard of changing regimens ($p=0.008$). For example, the hazard of regimen change for a 15 year-old starting cART was 1.71 times higher (95% CI 1.14–2.56) than for a 5 year-old starting cART, after controlling for other factors. The right panel of Figure 2 shows the predicted probability of changing regimens as a function of age. Year of cART initiation and class of first cART were also strong predictors of regimen change in adjusted analyses ($p<0.01$). Higher hazards of regimen change were associated with earlier years of cART initiation (HR=1.30; 95% CI 1.07–1.58 for those who initiated cART in 2002 compared with 2006). In addition, non-PI regimens had lower hazards of regimen change when compared with PI-based regimen (HR=0.47; 95% CI 0.34–0.66). In addition, lower baseline CD4 count was strongly associated with regimen change (HR=1.29; 95% CI 1.13–1.48 for CD4 counts of 100 compared with 350 cells/mm³).

Discussion

Treatment outcomes of HIV-infected children on initial cART in the Caribbean, Central and South America were disappointing. The majority of children initiated a NNRTI-based regimen at advanced stages of disease progression and immunosuppression. Risk of mortality during the first 5 years of treatment was significant. Mortality also tended to be higher among younger children (i.e., <5 years), although there was some evidence suggesting that adolescents also were at higher risk. These findings are similar to those reported in a systematic review of 30 pediatric ART programs in sub-Saharan Africa,¹⁴ reflecting, perhaps, that pediatric HIV programs in the Americas face some of the same challenges seen in African programs including failures in PMTCT, and among HIV-infected infants, late diagnosis and initiation of cART, and high subsequent LTFU.

At 5 years of treatment, approximately 70% of participants remained on initial cART regimens. The incidence of changing regimens tended to be higher for older children. The durability of the first-line regimen in our study is comparable with what has been reported

for pediatric populations in both high- and low-income settings,^{15–17} emphasizing good responses to first-line cART in children regardless of type of regimen and initiation at later stages of disease. NNRTI-based cART had lower risks of change than protease inhibitor-based regimens in our children.

Regimen change rates decreased over calendar time in children starting ART in the Caribbean, Central and South America. Possible reasons include more tolerable and effective drugs, improved pediatric formulations, earlier initiation of treatment, better management of HIV and co-morbidities, and better adherence over time. Changes in national and international pediatric treatment guidelines during the study period may also have influenced this finding, especially after 2009–10 when programs adopted universal treatment to infants and higher CD4 thresholds for cART initiation. The parabolic shape of the predicted incidence of mortality as a function of age, with those starting cART between ages 5–10 years having the lowest risk of death, may have several explanations. The youngest children placed on cART may have been initiated due to rapid clinical deterioration, such that they were systematically different from the comparatively healthier children placed on cART at a later age. In addition, if younger aged children died of serious childhood diseases without being diagnosed with HIV and/or placed on cART, then they would be absent from the older cohort; this would be a second reason why older children might be less likely to include the rapid progressors that were included in the younger cohort.¹⁸

There is very little data on the experience of pediatric patients starting cART in Latin America and the Caribbean. Our observed risks of mortality for very young HIV-infected children are substantially lower than those estimated using the HIV Paediatric Prognostic Markers Collaborative Study risk calculator, which was derived using data in the absence of cART in United States and European cohorts.¹⁹ For example, the 1-year predicted probability of mortality for a child diagnosed with HIV at 1 year of age with CD4=200 cells/mm³ was 0.38 using the risk calculator, whereas this predicted probability in our Latin American cohort of cART initiators (holding all other covariates at their medians/modes) was 0.16. However, the observed risk of mortality for older children starting cART in our cohort was substantially higher than predicted by the risk calculator in the absence of cART in the developed world. For example, the 1-year predicted probability of mortality for a child diagnosed with HIV at the age of 10 years with CD4=200 cells/mm³ was 0.01 using the risk calculator, whereas it was 0.07 based on our data. Although such comparisons are flawed, they perhaps help illustrate both the successes and challenges for perinatally-infected children in Latin America during the cART era.

That half of the children in the cohorts started cART over the age of 5 years is a concern for PMTCT programs in the Americas. The CHER study demonstrated the superiority of immediate cART over delayed treatment for infected infants.²⁰ Yet therapy for infants under the age of 3 months was the exception in our six clinic cohorts, not the rule. Infants born with HIV infection indicates sub-optimal functioning of the clinical and public health PMTCT paradigm.

LTFU was higher for older children, and actually seemed to accelerate after longer times on treatment for older children. This result may be a reflection of the challenges of retaining adolescents in care.²¹ It is also possible that there was “treatment fatigue” and that parents or guardians stopped therapy in apparently healthy HIV-infected children. The literature for Latin America and the Caribbean suggests many causes for non-adherence, primarily among adults: stigma, access to care, denial, drug side effects, lack of appreciation that drugs can help persons who are asymptomatic, depression, substance use, inattentive parenting, illness or death of a mother, health system disarray, poverty, transportation, and others.^{22–35} It is also plausible that over time children’s families moved and the children either went off of therapy or entered into ART programs elsewhere and this was not captured in our cohorts.¹⁵

Study strengths include the inclusion of diverse cohorts from six venues in Argentina, Brazil (2 sites), Haiti, and Honduras (2 sites), the inclusion of 1174 children, and our strong statistical methods to maximize the utility of clinical data. Limitations of our study include missing data in our real-world settings, tiny numbers of children (13 and 17) from two of the six sites, and a lack of detail as to why some children were lost to follow-up. Data on cause of death were also unavailable, as were maternal information (e.g., mother’s age, duration of HIV-infection, and clinical outcomes) and population genetics data. Expanding the utility of clinical databases to include social determinants and to link maternal and pediatric databases are goals of our CCASAnet network, as well as improving the quality and completeness of data collection.^{36–37}

Our study from diverse cohorts in Argentina, Brazil, Haiti, and Honduras suggests the urgency of need for quality improvement for PMTCT, maternal and child HIV programs, and early pediatric care in Latin America and the Caribbean. Our challenges are not unique, and are experienced in both high- and low-income settings.^{38–39} The management of a chronic, lifelong, incurable infectious disease in the context of stigma and poverty is challenging for parents and practitioners alike; innovative approaches are needed in the Americas and the Caribbean.^{40–44}

Acknowledgments

We thank additional members of the CCASAnet Pediatric team: Carina Cesar MD (Fundacion Huesped, Buenos Aires, Argentina); Flavia Ferreira MD, and Marcelle Maia PhD (Federal University of Minas Gerais, Belo Horizonte, Brazil); Aída Gouvêa MD, and Fabiana Carmo MD (Federal University of São Paulo, São Paulo, Brazil).

Supported by the National Institute of Allergy and Infectious Diseases, with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Cancer Institute, through cooperative agreement with the Vanderbilt University School of Medicine (U01 AI069923 [to C.M]).

Abbreviations

HIV

human immunodeficiency virus

cART

combination antiretroviral therapy

CCASAnet

Caribbean, Central and South America network

CDC

U.S. Centers for Disease Control and Prevention

AIDS

acquired immune deficiency syndrome

US

United States

PLHIV

persons living with HIV

PMTCT

prevention of mother-to-child transmission of HIV

HF-Argentina

Hospital Fernandez, Buenos Aires, Argentina

UFMG-Brazil

Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

UNIFESP-Brazil

Universidade Federal de São Paulo, São Paulo, Brazil

GHEKIO-Haiti

Le Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes, Port-au-Prince, Haiti

HE-Honduras and IHSS-Honduras

Hospital Escuela Universitario and Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras

VDCC

CCASAnet Data Coordinating Center at Vanderbilt University

LTFU

lost to follow-up

CD4 percent

percentage of CD4+ T lymphocytes

CD4 count

Absolute CD4+ T lymphocyte count

WHO

World Health Organization

PI

protease inhibitor

NRTI

nucleoside reverse transcriptase inhibitor

NNRTI

non-nucleoside reverse transcriptase inhibitor

IQR

interquartile range

HR

hazards ratio

CI

confidence interval

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Figure 1. Estimated cumulative incidence (and 95% confidence intervals) for mortality, loss to follow-up, and regimen change after cART initiation.

Figure 2.

Predicted probability of mortality, loss to follow-up, and regimen change 5 years after cART initiation based on age at cART initiation. For these predictions, all other covariates are set at their medians/modes (i.e., female sex, CD4 of 472 cells/mm³, year of cART 2005, first regimen class not PI-based, not having clinical AIDS at baseline, and study site as GHESKIO-Haiti). Pointwise 95% confidence intervals are illustrated with dashed curves.

Figure 3.
(online). Median age at cART initiation by year of cART initiation overall and by site. Dot size is proportional to the number of patient starting cART in a given year.

Table 1

Demographics, laboratory measurements and clinical factors at cART initiation, and follow-up information by site.

	HF-Argentina N=17	UFMG-Brazil N=255	UNIFESP-Brazil N=84	GHESKIO-Haiti N=615	HE-Honduras N=190	IHSS-Honduras N=13	Combined N=1174
Age at cART initiation (years)	5.8 (3.7, 7.8)	3.6 (1.1, 6.8)	2.5 (0.8, 5.7)	5.9 (2.0, 10.1)	5.1 (2.6, 7.8)	1.9 (1.3, 2.9)	4.7 (1.7, 8.8)
Age at HIV diagnosis (years)	3.3 (0.8, 5.8)	2.3 (0.7, 4.6)	1.2 (0.0, 4.6)	4.3 (1.5, 8.5)	3.4 (1.4, 6.5)	1.3 (1.1, 2.5)	3.3 (1.0, 7.0)
Male	47% (8)	50% (128)	44% (37)	46% (285)	49% (91)	46% (6)	47% (555)
Months from enrollment to first cART	1.6 (0.3, 3.3)	5.1 (1.9, 17.6)	2.3 (1.2, 9.9)	4.4 (1.6, 18.3)	0.3 (0.0, 1.6)	0.0 (0.0, 0.3)	3.4 (1.1, 14.1)
Year of first cART	2005 (*02, *08)	2004(*02, *08)	2000 (*99, *04)	2007 (*04, *10)	2004 (*03, *07)	2005 (*04, *06)	2005 (*03, *09)
First cART class							
PI-based	53% (9)	56% (143)	54% (45)	2% (10)	10% (19)	0% (0)	19% (226)
Other	47% (8)	44% (112)	46% (39)	98% (605)	90% (171)	100% (13)	81% (948)
Baseline CD4 count (cells/mm ³)	494 (344, 791)	573 (298, 955)	664 (365, 1285)	461 (174, 892)	350 (124, 650)	606 (93, 994)	472 (201, 902)
Missing baseline CD4 count	29% (5)	13% (32)	12% (10)	5% (32)	18% (34)	38% (5)	10% (118)
Baseline CD4 percent	25.5 (14.9, 30.2)	18.1 (11.8, 25.1)	24.2 (16.6, 34.6)	14.1 (7.3, 20.0)	14.8 (8.3, 21.4)	–	16.1 (9.7, 23.4)
Missing baseline CD4 percent	29% (5)	14% (36)	33% (28)	35% (215)	99% (188)	100% (13)	41% (485)
Baseline HIV-1 RNA (log ₁₀ copies/mL)	5.1 (4.6, 5.7)	4.9 (4.3, 5.7)	4.6 (3.7, 5.5)	–	4.8 (4.3, 5.2)	5.0 (3.8, 5.0)	4.9 (4.1, 5.6)
Missing baseline HIV-1 RNA	18% (3)	13% (33)	1% (1)	100% (614)	84% (160)	31% (4)	69% (815)
Clinical AIDS							
not AIDS	59% (10)	64% (162)	46% (39)	60% (366)	63% (120)	62% (8)	60% (705)
AIDS	18% (3)	35% (88)	14% (12)	40% (248)	35% (67)	31% (4)	36% (422)
Unknown	24% (4)	2% (5)	39% (33)	0% (1)	2% (3)	8% (1)	4% (47)
Follow-up time (years)	5.8 (2.3, 8.4)	7.5 (2.9, 10.6)	11.0 (5.3, 14.8)	3.8 (1.7, 7.3)	8.0 (5.5, 10.0)	5.6 (2.6, 7.4)	5.6 (2.3, 9.3)
Died	0% (0)	5% (13)	13% (11)	16% (100)	7% (14)	0% (0)	12% (138)
Lost to follow-up	53% (9)	22% (56)	19% (16)	18% (109)	27% (52)	62% (8)	21% (250)

Continuous variables reported with median (interquartile range); categorical variables reported with percent (number). Abbreviations: cART: combination antiretroviral therapy; HF-Argentina: Hospital Fernandez, Buenos Aires, Argentina; UFMG-Brazil: Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; UNIFESP-Brazil: Universidade Federal de São Paulo, São Paulo, Brazil; GHESKIO-Haiti: Le Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes, Port-au-Prince, Haiti; HE-Honduras: Hospital Escuela, Tegucigalpa, Honduras; IHSS-Honduras: Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras.

Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for mortality, loss to followup, and regimen change after cART initiation based on factors at cART initiation. Hazard ratios are adjusted for all other variables in the table and stratified by study site.

Table 2

	Mortality			Loss to followup			Regimen Change		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Baseline age (years)			<0.001			<0.001			0.008
0.5	2.60	(1.60, 4.22)		0.88	(0.59, 1.31)		0.87	(0.63, 1.21)	
1	2.29	(1.50, 3.48)		0.89	(0.63, 1.25)		0.89	(0.67, 1.17)	
2	1.78	(1.33, 2.38)		0.91	(0.72, 1.15)		0.91	(0.75, 1.10)	
5	1.00			1.00			1.00		
10	0.92	(0.74, 1.14)		1.42	(1.19, 1.69)		1.28	(1.09, 1.50)	
15	1.33	(0.74, 2.41)		2.23	(1.41, 3.51)		1.71	(1.14, 2.56)	
Sex			0.26			0.98			0.20
Male	1.21	(0.87, 1.70)		1.00	(0.78, 1.29)		1.15	(0.93, 1.41)	
Female (ref)	1.00			1.00			1.00		
Baseline CD4 count (cells/mm ³)			<0.001			0.005			<0.001
100	1.72	(1.38, 2.13)		1.07	(0.91, 1.27)		1.29	(1.13, 1.48)	
200	1.29	(1.17, 1.42)		1.02	(0.94, 1.10)		1.13	(1.06, 1.20)	
350 (ref)	1.00			1.00			1.00		
500	0.87	(0.82, 0.92)		1.03	(0.98, 1.07)		0.94	(0.90, 0.97)	
Year of first cART			0.39			0.10			0.005
2002	0.78	(0.49, 1.25)		0.76	(0.55, 1.03)		1.30	(1.07, 1.58)	
2004	0.94	(0.79, 1.11)		0.88	(0.78, 0.99)		1.14	(1.05, 1.23)	
2006 (ref)	1.00			1.00			1.00		
2008	0.93	(0.79, 1.09)		1.09	(0.96, 1.24)		0.88	(0.77, 1.00)	
2010	0.79	(0.52, 1.18)		1.16	(0.84, 1.60)		0.77	(0.56, 1.06)	
2012	0.65	(0.32, 1.30)		1.22	(0.71, 2.10)		0.67	(0.39, 1.15)	
First cART regimen class			0.14			0.56			<0.001
PI-based (ref)	1.00			1.00			1.00		
Other	0.58	(0.28, 1.20)		1.13	(0.74, 1.74)		0.47	(0.34, 0.66)	
Clinical AIDS at baseline			0.002			0.85			0.27

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	Mortality				Loss to followup				Regimen Change			
	HR	95% CI	P		HR	95% CI	P		HR	95% CI	P	
not AIDS	1.00				1.00				1.00			
AIDS	1.88	(1.31, 2.69)			0.93	(0.70, 1.22)			1.20	(0.96, 1.50)		
Unknown	0.95	(0.29, 3.14)			1.05	(0.52, 2.13)			1.13	(0.69, 1.85)		