Published in final edited form as:
J Acquir Immune Defic Syndr. 2013 February 1; 62(2): 208–219. doi:10.1097/QAI.0b013e31827b70bf.

Outcomes of antiretroviral therapy in children in Asia and Africa: a comparative analysis of the IeDEA pediatric multiregional collaboration

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Abstract

Background—We investigated 18-month incidence and determinants of death and loss-to-follow-up of children after antiretroviral therapy (ART) initiation in a multiregional collaboration in lower-income countries.

Methods—HIV-infected children (positive PCR <18 months or positive serology ≥18 months) from IeDEA cohorts, <16 years, initiating ART were eligible. A competing risk regression model was used to analyze the independent risk of two failure types: death and loss-to-follow-up (>6 months).

Findings—Data on 13611 children, from Asia (N=1454), East-Africa (N=3114), Southern-Africa (N=6212) and West-Africa (N=2881) contributed 20,417 person-years of follow-up. At 18 months, the adjusted risk of death was 4.3% in East-Africa, 5.4% in Asia, 5.7% in Southern-Africa

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*See the International Epidemiologic Databases to Evaluate AIDS (IeDEA) composition in the Appendix

Presented in part to the XVIII International AIDS Conference, July 19-23 2010, Vienna Austria, Abstract-MOAB0202

Conflict of Interest: There are no conflicts of interest to declare.

and 7.4% in West-Africa (P=0.01). Age<24 months, WHO stage 4, CD4<10%, attending a private sector clinic, larger cohort size and living in West-Africa were independently associated with poorer survival. The adjusted risk of loss-to-follow-up was 4.1% in Asia, 9.0% in Southern-Africa, 14.0% in East-Africa, and 21.8% in West-Africa (P <0.01). Age<12 months, non NNRTI-based ART regimen, WHO stage 4 at ART start, ART initiation after 2005, attending a public sector or a non-urban clinic, having to pay for laboratory tests or antiretroviral drugs, larger cohort size, and living in East or West-Africa were significantly associated with higher loss-to-follow-up.

Conclusion—Findings differed substantially across regions but raise overall concerns about delayed ART start, low access to free HIV-services for children, and increased workload on program retention in lower-income countries. Universal free access to ART services and innovative approaches are urgently needed to improve pediatric outcomes at program level.

Keywords

antiretroviral therapy; children; cohort studies; HIV infection; mortality; loss to follow-up; low income countries; Asia; Africa

Introduction

The HIV pediatric epidemic continues to expand (1), with an estimated 3.4 million children under 15 years of age living with HIV as of December 2010. However, while great strides have been made to expand access to care for adults, access and use of pediatric antiretroviral therapy (ART) have lagged behind (1). Providing ART to children poses unique challenges to HIV care programs. This may be due to weak linkage between prevention of mother-to-child transmission (PMTCT) and child health services, poor access to HIV diagnostic tests in children, and complexities of infant and child HIV care differing from those generally encountered among adults. Limited access to pediatric antiretroviral drugs and availability of drugs in appropriate formulations as well as the reliance on an individual other than the patient themselves to provide the medications are only a few of the challenges (2, 3). Thus, overall, at the end of 2010 only 23% of the estimated 2020 000 HIV-infected children <15 years of age eligible for ART were treated in low- and middle-income countries, with coverage rates varying from 2% in Sudan to 88% in Botswana (1, 4).

Characteristics at ART initiation and short-term outcomes (mortality, retention in program) are evolving in pediatric ART programs. Recent reports show decreased mortality in children after ART initiation (5-12) but children continue to initiate ART with advanced disease (13, 14). In addition, programs that have rapidly scaled-up ART have, as in adults, high loss to follow-up (LTFU) rates (6). In adults, high rates of LTFU correspond to underreported mortality (15, 16) suggesting that in children a significant proportion of child mortality may be unseen as well. Several site-specific and individual patient factors could explain the heterogeneity in effectiveness of HIV-care program outcomes (17). However, factors associated with mortality and cohort attrition in children have received little attention to date and need further investigation in order to evaluate the impact of ART scale-up on pediatric outcomes at the program level (17).

In 2006, the US National Institutes of Health launched the International epidemiologic Databases to Evaluate AIDS (IeDEA) initiative to better describe trends in HIV epidemiology in the context of ART access by region of the world (http://www.iedea-hiv.org). As part of the pediatric component of the IeDEA multiregional collaboration, we have combined data across four resource-constrained IeDEA regions to study 18-month mortality and loss-to-follow-up rates after ART initiation and explore their baseline individual and site-specific determinants.

Methods

Ethics statement

Each participating pediatric HIV clinic formally agreed to be included in the IeDEA collaboration, with local Institutional Review Board and NIH approval.

Study design

We conducted a multiregional cohort analysis within the IeDEA collaboration. All clinical centers from four (Asia-Pacific, East-Africa, Southern-Africa, and West-Africa) of the six IeDEA Collaboration regions collecting data on pediatric HIV care were eligible.

Study population

All HIV-infected children (positive PCR <18 months or positive serology ≥18 months) aged <16 years at ART initiation, with documented gender, who were ART-naïve (except for exposure to perinatal PMTCT prophylaxis) and who initiated ≥3 antiretroviral drugs from November 21th 1995 (first ART initiation in Asia-Pacific) to June 24th 2009 were included irrespective of the first-line ART regimen. The database was closed on December 20th 2009.

Each ART program within the consortium has its own protocol for clinical follow-up and laboratory testing. However, HIV-infected children were typically seen in clinics at least every three months, and their CD4 count measured every six months to monitor their immunological response to ART. Routine viral load monitoring was not available at most sites.

Outcomes

The outcomes of interest were i) mortality, defined as a death documented in the database; ii) loss-to-follow-up, defined as failure to return to clinic for >6 months after the last clinic visit was reported in the database, the closing date of the database was >6 months since that visit, and the child was not known to be dead or have transferred to another treatment site.

Key variables and definitions

Baseline was defined as the date of ART initiation. Follow-up was censored at the earliest of the following: date of last clinical contact up to 18 months on ART or date of transfer-out or date of death. Explanatory baseline factors included the following: gender, age, CD4 count and percent, year of ART initiation and first-line antiretroviral regimen (containing a non-nucleoside reverse transcriptase inhibitor [NNRTI]- or a protease inhibitor [PI]). The clinical stage of HIV disease was defined as either less advanced (CDC stage A/B or WHO stage I/II/III/) or advanced (CDC stage C or WHO stage IV).

Age at ART initiation was categorized in five groups: <12 months; 1-2 years; 3-4; 5-9 and ≥10 years. The severity of immunodeficiency was defined according to 2006 WHO criteria (18): CD4% <25% or CD4 count <1500 cells/mm^3 for children <12 months; CD4% <20% or CD4 count <750 cells/mm^3 for children between 12 and 35 months; CD4% <15% or CD4 count <350 cells/mm^3 for children between 36 and 59 months; CD4% <10% or CD4 count <200 cells/mm^3 for children ≥5 years. According to toxicity scales from the National Institute of Allergy and Infectious Diseases, severe anemia was defined as hemoglobin (Hb) <7 g/dL for children ≥57 days old. Baseline values for laboratory and clinical measurements were defined as the values closest to ART initiation that fell into a window of 90 days prior to ART initiation and 30 days after. Site-specific variables from a pediatric site survey conducted in 2009 were also analyzed (19): IeDEA region, rural versus urban site, length of clinic experience with provision of pediatric ART, clinic size (total number of children

included per site during the study period), family-centered care approach, use of generic drug combinations, free access to ARV drugs, free access to opportunistic infection (OI) prophylaxis, free access to laboratory tests, documentation of death events, lost-to-follow-up tracking system.

Data Management

In collaboration with participating sites, each IeDEA regional data center is responsible for the development of data collection systems, the establishment of mechanisms for receiving and combining data from individual sites, verifying data quality, harmonizing lists and definitions of variables. In addition, each regional data center develops and implements methods for analyzing cohort data and performs training on data collection, processing and cleaning. Four regional data sets were prepared and were transmitted to us by the regional data centers. These data were merged for the purpose of this analysis.

Statistical methods

Baseline categorical data are presented as frequencies (%) and continuous data as medians and interquartile ranges, (IQR). Continuous variables were compared using the Kruskal-Wallis test and categorical variables using Chi-Square or Fisher's exact tests. Heterogeneity of baseline differences between regions was tested. A competing risk model was used to analyze the independent risk of the two failures types: death and LTFU. LTFU is a competing cause of death, potentially increasing the risk of death because of ART interruption. Thus, assumptions about the independence of these two outcomes are not realistic. For this reason, we used a cumulative incidence function (CIF) to estimate the cumulative probability of each outcome over 18 months of follow-up (20). CIF were also estimated adjusted for baseline covariates.

To study correlates of the two outcomes, univariate analyses were first conducted. Second, we conducted multivariate competing risk analysis, using the Fine and Gray proportional sub-distribution hazard regression model using the R statistical software version 2.11.1 (*The R foundation for Statistical computing, Vienna, Austria*) with the *cmprsk* package (21, 22). Two multivariate models were created using this methodology. Variables were included in the full model if they were associated with each outcome in univariate competing risk analysis with $p<0.25$ (23). A final model was then created, by using a backward elimination procedure with a p-value less <0.05 considered statistically significant in the adjusted analysis. There was a substantial modification of the effect of the “search LTFU variable” in the full model. However, as sub-group analyses could not be run with too small sample sizes in some of the strata, we omitted the variable “search LTFU” from both mortality and LTFU models. The adjusted sub-distribution hazard ratios (asHR) were reported with their 95% confidence intervals (95% CI). Variables for which data were available on <70% of patients were not included.

Results

Description of sites

From 2000 to 2009, the collaboration included 54 pediatric clinical centers from four IeDEA regions with 13,611 children overall: 1454 from 11 Asian sites, 3,114 from 23 East-African sites, 6,162 from 10 Southern-African sites, and 2,881 from 10 West-African sites (Table 1). The sites were predominantly urban or semi-rural public sector clinics (Table 1). Significant between-region heterogeneity in site characteristics was observed. Asian and East-African cohort sites primarily had <250 children registered, while Southern and West-African cohort sites primarily had >500 active patients ($P<0.01$). Across these four regions, 93.8% of sites had free access to all laboratory tests and 93.3% had free access to first-line ART. Rates of

access to free OI prophylaxis were lower overall (83.3%) with substantial regional heterogeneity: 77.2% in Asia, 100.0% in East-Africa, 96.1% in Southern-Africa, and only 41.0% in West-Africa (P<0.001). Free access to second-line therapy was available for 87.8% of sites overall but in significantly fewer sites in West-Africa, 57.5% (P<0.001). Most sites (65.1%) traced children who were lost-to-follow-up using home visit and telephone calls with, again, substantial regional heterogeneity observed: 81.4% of Asian, 91.5% of East-African, 64.4% of Southern-African, and only 29.9% of West-African sites (P<0.001, Table1).

Characteristics of individual patients and antiretroviral regimens at ART initiation

At ART initiation, median age was 5 years (Interquartile range [IQR]: 2-9); median CD4 percentage was 12% (IQR: 7-18) with 51.8% of children being immunodeficient, and 19.9% having clinical AIDS. NNRTI-based regimens were the most common first-line antiretroviral drug regimens (76.9%), followed by those with a PI (20.1%), with other combinations accounting for the remaining 3%. These baseline patient characteristics differed significantly between regions (Table 1). Median CD4 percentage and age were 7% and 7 years respectively in Asia, 12% and 6 years in East-Africa, 14% and 4 years in Southern-Africa, and 13% and 5 years in West-Africa (P<0.001). More than 90% of children in Asia and East-Africa started ART with an NNRTI and two NRTIs, compared with 66.4% of children in Southern-Africa and 69.3% in West-Africa. The proportions of children initiating ART before 2005 were 40.0% in Asia, 6.4% in East-Africa, 21.6% in Southern-Africa, and 31.6% in West-Africa (P<0.001).

Mortality and loss to-follow-up rates across regions

Among 13,611 children followed up for a median length of 18 months (interquartile range: 7-32) and contributing 20,417 person-years of follow-up by 18 months after ART initiation, 5.7% of children had died, 12.3% were lost-to-follow-up, and 8.6% had transferred out of the clinic (Table 2). Mortality varied from 4.3% in East-Africa to 7.4% in West-Africa, while LTFU varied even more widely from 4.1% in Asia to 21.8% in West-Africa (P<0.001). Transfer-out rates varied from 0.4% of children in East-Africa to 16.4% in Southern-Africa (Table 2).

Overall, using a competing risk model with death and LTFU as competing events, the cumulative incidence rates of death were 4.5% (95% CI 4.2-4.8), 5.5% (95% CI 5.1-5.9), and 6.3% (95% CI 5.9 to 6.7) at 6, 12 and 18 months respectively. The estimated crude cumulative incidence of death at 18 months was highest in West-Africa (7.9%, 95% CI 6.9-8.9), followed by Southern-Africa (6.2%, 95% CI 5.6-6.8), Asia (5.7%, 95% CI 4.7-7.0), and East-Africa (4.9%, 95% CI 4.2-5.8) (P<0.01). When adjusting for age, WHO clinical stage and CD4 at ART initiation, along with type of facility, and cohort size, the risk of death was 7.4% in West Africa, 5.7% in Southern Africa, 5.4% in Asia and 4.3% in East-Africa (P=0.02, Table 3).

The crude estimated 18-month LTFU rate was 23.5% (95% CI 21.9-25.1) in West-Africa, 16.4% (95% CI 14.9-17.8) in East-Africa, 10.8% (95% CI 10.0-11.7) in Southern-Africa, and 4.3% (95% CI 3.3-5.5) in Asia (P<0.01). When adjusting for age, WHO clinical stage and CD4 at ART initiation along with type of ART regimen, year of ART initiation, type of facility, free access to laboratory tests and to ARV, non-urban site, and cohort size, the risk of loss-to-follow-up was 21.8% in West-Africa, 14.0% in East-Africa, 9.0% in Southern-Africa and 4.1% in Asia (P <0.01, Table 3).

Factors associated with the risk of dying

The crude estimated 18-month cumulative mortality was significantly higher in children <**24** months old at baseline, compared to older children (P<0.01, Figure 1). It was also significantly higher (10.5%) in children with severe immunodeficiency (CD4 <10%) at baseline, compared to the other groups: 4.7% in those with CD4 [10%-20% [, 4.5% in those with CD4 ≥20% and 5.4% in those with unknown CD4 percentage (P<0.01, Figure 2). We observed a significantly higher mortality in clinics with no LTFU search compared to those with any search in univariate analysis (Table 4 of the supplemental digital content).

The adjusted statistical analysis using a competing risk model (Table 3, and Table 4 of the supplemental digital content) identified the following individual baseline correlates of higher 18-month risk of dying (asHRs and their 95% CIs): age <12 months (asHR 2.8; CI: 2.2-3.5) P < 0.01) and age 1-2 years (asHR 1.5; CI: 1.2-2.0, P < 0.01) compared to 10-15 years (the reference group); clinical AIDS or stage-4 disease versus earlier stages (asHR 2.1; CI:1.8-2.5, P < 0.01); CD4% <10% versus ≥20% (asHR 3.0; CI:2.3-3.9, P < 0.01) or missing CD4% (asHR 1.5; CI:1.2-2.0, P < 0.01). Site-specific variables associated with higher mortality were the following: attending a private facility (asHR 1.5; CI:1.1-2.0, P < 0.01) or an unknown type of facility (asHR 2.4; CI:1.6-3.8, P < 0.01) compared to a public sector one; being followed-up in a large size cohort (500 to 800 children) (asHR 1.8; CI: 1.4-2.3, P < 0.01) compared to <250 children; receiving care in West-Africa, the site of highest mortality (asHR 1.3; CI:1.0-1.7, P= 0.04) compared to East-Africa the region with the lowest mortality rates. Mortality in Southern-Africa and Asia did not differ from East-Africa. No other pairwise regional comparison was statistically significant when adjusting for all other patient-level and site-specific predictors.

Factors associated with loss to follow-up

The crude estimated 18-month cumulative incidence of LTFU was significantly higher in children <24 months at baseline compared to older children (P<0.01, Figure 1) as well as in children with CD4 percentage ≥20% or unknown percentage at baseline, compared to those with CD4 percentage <20% (P<0.01, Figure 2). In the adjusted statistical analysis, a number of patient-level and site-specific factors were identified as independent predictors of higher LTFU hazards adjusted for the competing risk of death (Table 3, and Table 5 of the supplemental digital content): age < 12 months versus 10 to 15 years (asHR 1.6; CI: 1.4-2.0, P < 0.01); having received a first-line PI-based ART (asHR 1.4; CI:1.2-1.7, P < 0.01); or another regimen (asHR 1.7; CI: 1.3-2.1, P < 0.01) versus an NNRTI-based regimen; having clinical AIDS or stage-4 disease (asHR 1.4; CI:1.2-1.6, P < 0.01); or unknown AIDS staging (asHR 1.7; CI: 1.5-2.0, P < 0.01) versus non AIDS stage; having started ART in 2005-2007 (asHR 2.4; CI: 2.0-2.8), P < 0.01); or having started ART after 2007 (asHR 3.4 (2.9-4.1), P < 0.01) versus having initiated therapy before 2005; receiving care in a non-urban clinic (asHR 1.7; CI: 1.4-1.9, P < 0.01) versus being treated at an urban clinic; having to pay for laboratory tests (asHR 2.6, 95% CI 1.9-3.5, P < 0.01) versus receiving free access to laboratory tests and having to pay for first-line antiretrovirals (asHR 5.0, 95% CI 3.4-7.3, P < 0.01) versus having access to free ART; being a member of a larger cohort (i.e., one with 500 to 800 children) (asHR 1.8, 95% CI 1.5-2.3, P <00.1) versus a smaller cohort (< 250 children); and receiving care in East-Africa (asHR 3.5, CI:2.6-4.7, P < 0.01), or in West-Africa (asHR 3.1, CI:2.2-4.3, P < 0.01) versus Asia the region with the lowest rates of LTFU (Table 5).

Predictors of a less frequent LTFU were as follows: having CD4% [10-20% [(asHR 0.8; CI: 0.7-1.0, P = 0.03) versus ≥20%; receiving care in a private clinic (asHR 0.2 CI: 0.1-0.3, P < 0.01) rather than a public clinic, and cohort size [250-500[(asHR 0.8 CI: 0.6-0.9, P < 0.01).

Discussion

As HIV treatment is rapidly scaled up towards universal access in the first decade of the 21st century, the IeDEA multiregional pediatric collaboration provides a unique opportunity to monitor, analyze and compare children's outcomes taking into account patient and program-level factors while accounting for regional heterogeneity in these factors, in large scale care and treatment programs in low and middle-income countries. This analysis included 13,611 children contributing with 20,417 child-years of follow-up in a large number of pediatric cohorts. Overall cumulative mortality was measured at 5.7%, while LTFU rate was 12.3% after 18 months on ART, with marked differences of these estimates between the four regions studied: Asia, East-Africa, West-Africa, and Southern-Africa.

There are important observations gleaned from our study. Firstly, the 18-month mortality in children on ART is much lower than reported mortality estimates among untreated children before the ART era (24, 25), arguing for a clear benefit of ART as a pediatric HIV intervention. Our mortality estimates are consistent with previous reports of studies conducted among HIV-infected children on ART in resource constrained countries with reported mortality rates, ranging from 6.3% to 11.5%, usually obtained in small-size cohorts and in the early periods of the ART scale-up (5, 7, 9-14, 26). Despite heterogeneity between regions, our findings consistently reflect the impact of overall delayed ART initiation in children when adjusting for individual, programmatic and regional factors. Indeed, independent individual predictors of residual mortality on ART (advanced clinical stage of HIV disease, and severe immunosuppression) reflect late access to ART. In addition, most (71%) deaths in this data set occurred within the first six months after ART initiation, advocating for earlier and increased access to ART initiation in the pediatric population. These findings are consistent with those reported in previous studies (5, 7, 9-14) and in individual IeDEA regions (8, 26-28). A number of site-specific variables also explained part of the observed mortality: a greater cohort size increased mortality risk, possibly reflecting the impact of skilled health care staff shortages or work overload; receiving care in Western-Africa independently increased the mortality by 40% compared to East-Africa. While delayed ART initiation is common in all regions, there were significant differences in site-level factors such as having lower access to free HIV services in Western-Africa compared to other regions (laboratory tests, OI prophylaxis, first-line and second-line ART).

Secondly, the 18-month LTFU rates were unacceptably high and differed substantially across regions, with significant 3.5-fold and 3.1-fold increased hazards in East-Africa and West-Africa compared to the risk in Asia. Multiple sources of between-region heterogeneity could explain these higher LTFU rates including variations in a) operational definitions of LTFU and patient tracing systems, b) lack of access to free HIV services (laboratory tests, antiretroviral drugs and OI prophylaxis) in West-Africa compared to other regions, c) failure to accurately capture patient transfers as documented transfer-out rates differed significantly between regions, as very few transfers (<1%) were recorded in East and West Africa compared to 16% in Southern-Africa, d) levels of decentralization of HIV pediatric care out of urban hospitals, and e) reliability of drug supply chain management for non-NNRTI-based regimens, which are less affordable and accessible in East and West Africa compared to Southern-Africa. Requiring the patients' families to shoulder the fees for HIV care and clinical services was associated with higher LTFU rates as has previously been reported in adults (29).

In addition to patient-level and site-specific factors, our analysis illustrated the substantial impact of the large scale ART roll-out in lower-income countries over the past decade. Initiation of ART after 2005 and site cohorts with [500-800[children were associated with increased hazard of LTFU, while cohorts with less than 500 children had lower LTFU rates.

As antiretroviral treatment decreases mortality, we hypothesize that the number of HIV-infected children treated will continue to increase over time, particularly in regions where transfer-out rates are low, such as in East and West Africa. This substantial increase in the number of HIV-infected children followed in individual health facilities and the associated increased workload may further negatively impact the standard of care. Finally, the political instability and violence crisis could have also increased the rates of LTFU in East and West Africa, as this was recently investigated in Kenya (30).

We observed the seemingly contradictory finding that treatment at private clinics (where presumably care is not free) were associated with higher rates of death but lower rates of LTFU compared to being cared at public clinics (more frequently free of charge). While not explicitly measurable with these data, we suspect that this dichotomy may reflect that record-keeping practices may be better in private settings with a significantly higher mortality rates documented and lower LTFU rates compared to public settings, with a substantial proportion of excess LTFU being unreported mortality.

Limitations must be acknowledged in our study. The mortality rate we observed at 18 months is likely to be underestimated because of the high rates of LTFU, with a proportion of those lost more likely to die soon after defaulting from the program. Indeed, mortality has been commonly under-reported in African adult ART programs due to limited access to care and the frequent occurrence of death at home (16). The same finding was recently observed in children in East Africa where mortality and disclosure issues, including fear of family or community discrimination, were the most important reasons why children became lost-follow-up (31). Thus, it would be valuable to further ascertain outcomes at least in a sample of those children lost to follow-up in pediatric programs to correct the mortality rates as proposed in adults (32). Even though this information was available in a small number of cohorts in this study, this was not attempted here so our estimates are likely underestimating overall mortality rates, particularly in regions with high rates of LTFU. This means that pediatric outcomes may be much worse than reported, particularly in regions, such as East and West Africa, with both high mortality and LTFU rates.

When the cohort size is large, as in this case, statistical significance testing of baseline variables may produce highly significant statistical differences, even when they may have little clinical or programmatic implication. For example differences in gender between the regions was <5% (absolute), but was still highly statistically significant.

Data quality is another concern when analyzing such large collaborative datasets is. Lack of data completeness and substantial inter-study heterogeneity may reduce the accuracy of our results compared to studies coming from more homogeneous settings. Also, data on factors related to ART adherence or other social issues such as disclosure and orphan status, which were not generally available in our data, would help to better explain clinical outcomes in HIV-infected children. Smaller studies where these issues were documented have reported that disclosure is associated with ART adherence and needs to be monitored in programs (33). In addition, substantial rates of missing data on a number of target outcomes and their predictors and record-keeping practices have been varied over time and between regions. In the adjusted regression analyses, when missing variables were included as a separate category within variables, this may introduce bias in the effect estimates (34) and this was the reason why we did not included variables if missing data were > 70%.

Finally, our study may not be representative of all children on ART in these regions as most of the data were gathered from urban sites, in which the standard of care may be higher than in rural areas. Thus, we hypothesize that the programmatic deficiencies identified here could be worse in less structured clinical settings or at lower levels of the health care system.

Nevertheless, we are confident of our main findings, which raise significant operational concerns regarding the impact of both delayed ART start as measured by the high rates of advanced disease at the time of care initiation in our cohort, and the importance of long-term retention to care once enrolled into a program.

Despite the possibly superior level of care in our facilities, as well as concerns with missing data or quality of data collection, our mortality outcomes confirm that there is still a gap in achieving the standard of implementation of early ART in all HIV-infected children <2 years old as recommended in the 2010 WHO guidelines (35). Increasing early access to ART would decrease early on-ART mortality as demonstrated in the CHER trial (36). This is one of the primary operational challenges in pediatric care in these settings, pointing to the need for earlier identification of HIV-infected children, as soon as possible after birth, followed by expedited linkages from testing to ART initiation.

Retention in HIV care is one of the most important challenges faced by health care workers and HIV implementing partners as the coverage of HIV care and ART have improved for children in low-income countries (37). In the current study, high LTFU rates were associated with rapid scale-up, suggesting problems of adaptation of the health care organization and/or staff shortages. Evolving to smaller decentralized clinics rather than expanding large single programs and task shifting could result in increased access to ART services and good program outcomes as recently reported in Malawi (38, 39). Finally, LTFU was strongly associated with fees for ART services. This predictable finding, already reported in adults (29) underscores the urgent need for universal free access to all ART services for children too.

Future research should assess whether health systems are meeting the challenges of providing care linkages between all points on the HIV care continuum from early infant diagnosis, to ART initiation and long term retention of patients. It is also crucial to better document the causes of loss to program and to propose sustainable approaches to increase retention in HIV pediatric programs in lower-income countries.

With this aim, access to treatment through a family-centered approach should be considered. In this model, primary caregivers on treatment can be sources of continuity, knowledge, and strength for pediatric patients and other HIV-infected family members (40, 41).

Although data quality of such international data sets should be improved and documentation of clinical outcomes could have been more complete, this multiregional collaborative study offered a unique opportunity to improve our understanding of the rapidly expanding pediatric ART services taking into account both patient-level and site-specific factors. Such analyses should be repeated to explore secular trends in the second decade of wide ART use in these settings. Large-scale ART for children in resource-limited settings is feasible, but innovative and sustainable approaches are urgently required to improve early ART initiation, as well as retain children in ART programs in lower-income countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge all of the children and their families followed up in the participating pediatric centers. We also thank the staff from all participating pediatric centres. We warmly thank all the investigators and pediatric coordinators from the Pediatric IeDEA Regions contributing to the project: Asia (Annette Sohn), East-Africa (Kara Wools-Kaloustian), Southern-Africa (Mary-Ann Davies), Western Africa (Alain Azondekon) and the IeDEA Pediatric Working Group: Melanie Bacon, Rosemary McKaig, Robin Huebner, Lori Schwarze. We also thank

Denis Nash (Columbia University, Mailman School of Public Health) for helping with the regional site survey and Andrea Ciaranello for her helpful comments on earlier draft. Special thanks to Alioum Ahmadou (ISPED) for his statistical advice.

This study was led by the IeDEA West-Africa Group (principal investigators: François Dabis, Emmanuel Bissagnéné); Bordeaux staff: Eric Balestre, Didier K. Ekouévi, Charlotte Lewden, Valériane Leroy, Karen Malateste, Elodie Rabourdin, Rodolphe Thiebaut. Abidjan staff: Gérard Allou, Jean-Claude Azani, Patrick Coffie, Hughes Djétouan, Bertin Kouadio.

The International Epidemiological Databases to Evaluate AIDS in West-Africa (IeDEA West-Africa) is supported by: the National Cancer Institute (NCI), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Allergy And Infectious Diseases (NIAID) as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) (Grant no. 5U01AI069919-01 to 04). The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Appendix

Appendix:

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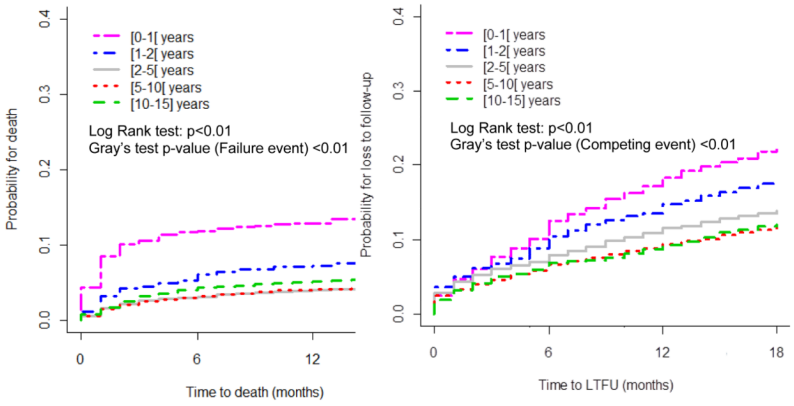
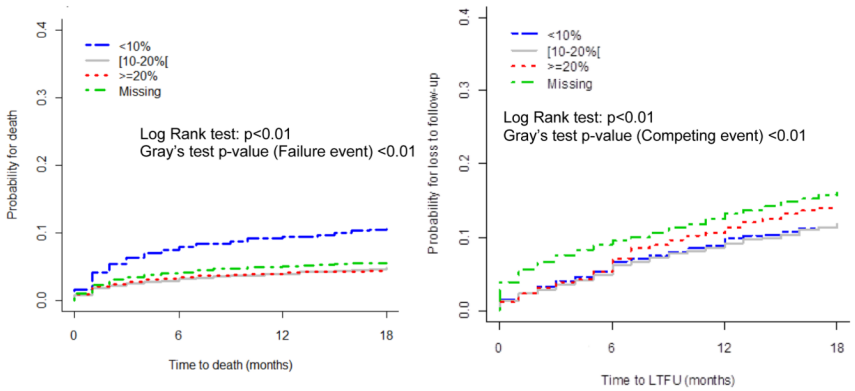


	Death M18 *			LTFU M18 *		
	M6	M12	M18	M6	M12	M18
Age at ART initiation						
<12 months	11.8 (10.2-13.5)	12.9 (11.2-14.6)	13.8 (12.0-15.6)	12.4 (10.8-14.2)	18.3 (16.3-20.5)	22.2 (19.9-24.5)
[1-2 years[	6.0 (4.9-7.3)	7.2 (5.9-8.6)	8.0 (6.6-9.5)	10.4 (8.9-12.0)	14.8 (12.9-16.7)	17.8 (15.8-20.0)
[2-5 years[	3.1 (2.5-3.7)	4.0(3.3 -4.7)	4.3 (3.7-5.1)	7.8 (7.0-8.8)	11.5 (10.5-12.7)	13.9 (12.7-15.1)
[5-10 years[	3.2 (2.7-3.7)	4.1 (3.5-4.7)	4.7 (4.1-5.4)	6.6 (5.9-7.3)	9.3 (8.5-10.2)	11.7 (10.7-12.7)
[10-15 years]	4.3 (3.5-5.2)	5.1 (4.2-6.1)	6.2 (5.1-7.3)	6.8 (5.8-7.9)	9.3 (8.0-10.5)	12.0 (10.5-13.5)

* Cumulative incidence function expressed as % with 95% Confidence Intervals

Figure 1.

Estimated cumulative incidence curves with death (left panel) and loss to follow-up (LTFU) (right panel) as competing events in 13611 children on antiretroviral therapy (ART), by **age group at ART initiation** in the IeDEA pediatric collaboration database.



	Death M18 *			LTFU M18 *		
	M6	M12	M18	M6	M12	M18
%CD4 at ART initiation						
<10%	7.9 (6.9-8.9)	9.3 (8.2-10.5)	10.5 (9.3-11.8)	6.6 (5.7-7.6)	9.8 (8.7-11.0)	11.8 (10.5-13.1)
[10-20%[	3.1 (2.5-3.9)	3.9 (3.2-4.7)	4.7 (3.9-5.6)	6.1 (5.3-7.1)	9.1 (8.1-10.3)	11.8 (10.5-13.1)
≥20%	3.4 (2.6-4.5)	4.1 (3.1-5.2)	4.5 (3.5-5.8)	7.1 (5.8-8.5)	11.3 (9.7-13.1)	13.9 (12.1-15.9)
Missing	4.1 (3.7-4.6)	5.0 (4.5-5.6)	5.4 (4.9-6.0)	9.5 (8.8-10.3)	13.1 (12.3-14.0)	16.0 (15.1-17.0)

* Cumulative incidence function expressed as % with 95% Confidence Intervals

Figure 2. Estimated cumulative incidence curves with death (left panel) and loss to follow-up (LTFU) (right panel) as competing events in 13611 children on ART, by CD4% at ART initiation in the IeDEA pediatric collaboration database

Table 1

Summary of baseline characteristics and site description by IeDEA region (N=13,611 children in 54 clinics). IeDEA pediatric multi-regional collaboration. 2000-2009.

	Asia	East-Africa	Southern-Africa	West-Africa	TOTAL	Test for between-region heterogenity *P*
Individual baseline characteristics by IeDEA region						
N	1454	3114	6162	2881	13611	
Boys, %	50.3	52.2	50.6	55.1	51.9	<0.01
Median age (years) (IQR)	7 (4; 10)	6 (3; 9)	4 (2; 8)	5 (2; 9)	5 (2; 9)	<0.01
Age at ART initiation, %						<0.01
< 1 year	6.9	4.5	17.7	6.7	11.2	
[1-2[years	6.3	9.2	13.0	11.4	11.1	
[2-5[years	18.1	29.4	24.8	29.3	26.1	
[5-10[years	44.4	37.8	31.6	34.9	35.1	
[10-15] years	24.2	19.1	12.8	17.7	16.5	
Initial ART regimen, %						<0.01
2 NRTI+1 NNRTI	93.4	97.0	66.4	69.3	76.9	
2 NRTI+1 PI	0.9	0.9	30.1	29.3	20.1	
Other	5.7	2.1	3.5	1.4	3.0	
Clinical stage, %						<0.01
A, B or I,II,III	48.6	61.3	50.2	37.0	49.8	
AIDS or IV	13.3	35.4	17.4	12.0	19.9	
Not used, unknown	38.1	3.3	32.4	51.0	30.3	
Median weight-for-age Z-score (IQR)	−3 (−4; −1)	−2 (−4; −1	2 (−4; −1)	−3 (−4; −1)	−2 (−4; −1)	<0.01
Median CD4 percentage (IQR)	7 (2; 14)	12 (7; 16	14 (9; 21)	13 (7; 19)	12 (6; 18)	<0.01
Median Hb (IQR)	11 (9; 12)	11 (9; 12	10 (9; 11)	10 (8; 11)	10 (9; 11)	<0.01
Year of ART initiation, %						<0.01
<2005	40.0	6.4	21.6	31.6	22.2	
[2005;2007[	31.7	41.2	59.9	41.9	48.8	
≥2007	28.3	52.4	18.5	26.6	29.0	
Severe anemia (Hb<7g/dL), %						<0.01
Yes	2.6	2.4	1.2	4.4	2.3	
No	75.7	51.0	27.8	69.4	47.0	

	Asia	East-Africa	Southern-Africa	West-Africa	TOTAL	Test for between-region heterogenity *P*
Unknown	21.7	46.6	71.0	26.2	50.7	
Sites characteristics by IeDEA region						
Center, n	11	23	10	10	54	
N	1454	3114	6162	2881	13611	
Cohort size, %						<0.01
<250	73.7	45.7	9.1	18.4	26.4	
[250-500[	26.3	27.5	6.1	31.5	18.5	
[500-800[	0.0	0.0	41.0	50.1	29.2	
≥800	0.0	26.8	43.7	0.0	25.9	
Type of facility, %						<0.01
Public, Academic	85.0	99.8	90.0	77.1	89.0	
Private not for profit	8.9	0.2	6.1	22.9	8.6	
Unknown	6.1	0.0	3.9	0.0	2.4	<0.01
Free access to lab tests, %	86.0	100.0	96.1	86.0	93.8	<0.01
Free access to first-line ART, %	93.9	100.0	96.1	80.0	93.3	<0.01
Free access to second-line ART, %	93.9	96.5	96.1	57.5	87.8	<0.01
Free access to OI prophylaxis,%	77.2	100.0	96.1	41.0	83.3	<0.01
Location, %						<0.01
Urban	76.4	54.1	37.6	100.0	58.7	
Rural, semi-rural	17.5	45.9	58.5	0.0	38.8	
Missing	6.1	0.0	3.9	0.0	2.4	
Research LTFU, %						<0.01
Home visit and phone call	81.4	91.5	64.4	29.9	65.1	
Only phone call	4.7	8.1	29.9	22.5	20.7	
Only home visit (by clinic st by outreach workers)	7.8	0.4	1.8	0.0	1.8	
No phone call and no home visit	6.1	0.0	3.9	47.5	12.5	

ART: antiretroviral therapy, IQR: inter-quartile range, LTFU: lost to-follow-up, NNRTI: non nucleoside reverse transcriptase inhibitor, NRTI: nucleoside reverse transcriptase inhibitor, PI: protease inhibitor.

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2014 February 01.

Table 2

Death, transfer-out and loss to follow-up at 18-month after ART initiation by IeDEA region and cohort (N=13, 611). IeDEA pediatric multi-regional collaboration. 2000-2009.

Region	Cohort	Total	Transfer-out		Death		Loss to follow-up	
		N	N	%	N	%	N	%
Asia	1	240	54	22.5	9	3.8	3	1.3
	2	382	26	6.8	35	9.2	2	0.5
	3	114	1	0.9	10	8.8	10	8.8
	4	129	7	5.4	3	2.3	3	2.3
	5	186	8	4.3	4	2.2	9	4.8
	6	29	0	0.0	1	3.4	2	6.9
	7	73	6	8.2	1	1.4	4	5.5
	8	12	3	25.0	2	16.7	1	8.3
	9	68	1	1.5	7	10.3	2	2.9
	10	144	11	7.6	4	2.8	9	6.3
	11	77	0	0.0	3	3.9	14	18.2
Asia	Total	1454	117	8.0	79	5.4	59	4.1
East Africa	12	55	0	0.0	0	0.0	0	0.0
	13	173	0	0.0	11	6.4	49	28.3
	14	179	1	0.6	9	5.0	5	2.8
	15	280	0	0.0	11	3.9	28	10.0
	16	4	0	0.0	0	0.0	0	0.0
	17	35	0	0.0	2	5.7	2	5.7
	18	45	0	0.0	2	4.4	0	0.0
	19	64	0	0.0	0	0.0	7	10.9
	20	59	0	0.0	5	8.5	2	3.4
	21	323	1	0.3	15	4.6	27	8.4
	22	252	1	0.4	5	2.0	52	20.6
	23	46	0	0.0	2	4.3	2	4.3
	24	835	1	0.1	36	4.3	123	14.7

Region	Cohort	Total	Transfer-out		Death		Loss to follow-up	
		N	N	%	N	%	N	%
	26	55	0	0.0	3	5.5	0	0.0
	27	70	0	0.0	7	10.0	7	10.0
	28	178	0	0.0	9	5.1	16	9.0
	29	152	1	0.7	10	6.6	10	6.6
	30	8	0	0.0	0	0.0	0	0.0
	31	3	0	0.0	0	0.0	0	0.0
	32	3	0	0.0	0	0.0	0	0.0
	33	107	3	2.8	3	2.8	33	30.8
	34	108	5	4.6	1	0.9	64	59.3
East Africa	Total	3114	13	0.4	134	4.3	435	14.0
Southern Africa	35	240	0	0.0	18	7.5	3	1.3
	36	921	42	4.6	28	3.0	48	5.2
	37	212	23	10.8	1	0.5	2	0.9
	38	1774	102	5.7	74	4.2	89	5.0
	39	545	53	9.7	11	2.0	19	3.5
	40	622	157	25.2	21	3.4	54	8.7
	41	111	1	0.9	0	0.0	18	16.2
	42	378	31	8.2	24	6.3	9	2.4
	43	789	381	48.3	117	14.8	180	22.8
	44	570	223	39.1	56	9.8	135	23.7
Southern Africa	Total	6162	1013	16.4	350	5.7	557	9.0
West Africa	45	331	0	0.0	35	10.6	17	5.1
	46	178	0	0.0	5	2.8	57	32.0
	47	649	0	0.0	45	6.9	60	9.2
	48	251	12	4.8	22	8.8	25	10.0
	49	22	0	0.0	0	0.0	19	86.4
	50	794	0	0.0	67	8.4	213	26.8
	51	325	0	0.0	8	2.5	216	66.5
	52	79	0	0.0	8	10.1	1	1.3

Region	Cohort	Total	Transfer-out		Death		Loss to follow-up	
		N	N	%	N	%	N	%
West Africa	53	181	13	7.2	12	6.6	8	4.4
	54	71	6	8.5	12	16.9	13	18.3
	Total	2881	31	1.1	214	7.4	629	21.8
TOTAL		13611	1174	8.6	777	5.7	1680	12.3

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2014 February 01.

Table 3

Mortality and LTFU adjusted analysis using a competing risk model in 13611 children on antiretroviral therapy. IeDEA pediatric multi-regional collaboration. 2000-2009.

	Death at M18 (n=777) (%)	Mortality adjusted analysis			LTFU at M18 (n=1680) (%)	LTFU adjusted analysis		
		asHR *	CI (95%) **	*P*		asHR *	CI (95%) **	*P*
Individual variables								
Age at ART initiation				<0.01				<0.01
[10-15] years	5.5	Ref.	-	-	10.4	Ref.	-	-
[5-10[years	4.3	0.8	0.7-1.0	0.12	10.3	1.0	0.8-1.1	0.86
[2-5[years	4.0	0.8	0.6-1.1	0.16	12.3	1.0	0.9-1.2	0.58
[1-2[years	7.3	1.5	1.2-2.0	<0.01	15.5	1.1	0.9-1.4	0.15
<12 months	12.9	2.8	2.2-3.5	<0.01	18.5	1.6	1.4-2.0	<0.01
ART regimen at baseline		-	-	-				<0.01
2 NRTI+1 NNRTI	4.8				11.5	Ref.	-	-
2 NRTI+1 PI	9.1				14.5	1.4	1.2-1.7	<0.01
Other	7.3				19.3	1.7	1.3-2.1	<0.01
Clinical stage at ART initiation				<0.01				<0.01
A,B or I,II,III	4.1	Ref.	-	-	10.4	Ref.	-	-
AIDS or IV								
Unknown	5.4	1.1	0.9-1.4	0.23	14.5	1.7	1.5-2.0	<0.01
% CD4 at ART initiation				<0.01				<0.01
≥20%	4.2	Ref.	-	-	12.4	Ref.	-	-
[10-20%[	4.3	1.2	0.9-1.6	0.27	10.3	0.8	0.7-1.0	0.03
<10%	9.9	3.0	2.3-3.9	<0.01	10.6	0.9	0.8-1.1	0.54
Missing	5.0	1.5	1.2-2.0	<0.01	13.9	1.1	0.9-1.3	0.20
Year of ART initiation		-	-	-				<0.01
<2005	6.5				6.6	Ref.	-	-
[2005-2007[	6.1				13.8	2.4	2.0-2.8	<0.01
≥2007	4.4				14.2	3.4	2.9-4.1	<0.01
Programmatic variables								
Type of facility				<0.01				<0.01

	Death at M18 (n=777) (%)	Mortality adjusted analysis			LTFU at M18 (n=1680) (%)	LTFU adjusted analysis		
		asHR *	CI (95%) **	*P*		asHR *	CI (95%) **	*P*
Public	5.5	Ref.	-	-	13.3	Ref.	-	-
Private	7.8	1.5	1.1-2.0	<0.01	4.7	0.2	0.1-0.3	<0.01
Missing	7.0	2.4	1.6-3.8	<0.01	5.5	0.05	0.03-0.09	<0.01
Rural, semi-rural vs urban	6.1	-	-	-	12.6	1.7	1.4-1.9	<0.01
Pay laboratory tests vs fre	5.8	-	-	-	28.9	2.6	1.9-3.5	<0.01
Free OI prophylaxis					-	-	-	-
Free	5.4	-	-	-	10.4	-	-	-
Pay (partial or full)	7.8				26.5			
Not available	5.7				4.6			
Pay first line ART vs free	5.9	-	-	-	28.6	5.0	3.4-7.3	<0.01
Cohort size				<0.01				<0.01
<250	4.7	Ref.	-	-	10.7	Ref.	-	-
[250-500[	6.1	1.2	0.9-1.5	0.22	14.9	0.8	0.6-0.9	<0.01
[500-800[	8.0	1.8	1.4-2.3	<0.01	16.7	1.8	1.5-2.3	<0.01
≥800	3.9	1.1	0.8-1.4	0.59	7.4	0.9	0.7-1.1	0.43
Regional variable				<0.01				<0.01
Asia	5.4	1.0	0.7-1.4	0.87	4.1	Ref.	-	-
East Africa	4.3	Ref.	-	-	14.0	3.5	2.6-4.7	<0.01
Southern Africa	5.7	0.9	0.7-1.1	0.38	9.0	1.2	0.8-1.7	0.31
West Africa	7.4	1.3	1.0-1.7	0.04	21.8	3.1	2.2-4.3	<0.01

*asHR = adjusted subdistribution hazard ratio. **CI = confidence interval, ART: antiretroviral therapy, IQR: inter-quartile range, LTFU: lost to-follow-up, NNRTI: non nucleoside reverse transcriptase inhibitor, NRTI: nucleoside reverse transcriptase inhibitor, PI: protease inhibitor.