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Mortality and clinical outcomes in children treated with antiretroviral therapy in four African vertical programs during the first decade of paediatric HIV care, 2001-2010

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ABSTRACT

Background

Despite the progress made in expanding pediatric HIV care provision worldwide many children are diagnosed and start antiretroviral treatment (ART) late in sub-Saharan Africa.

Methods

Cohort analysis of data from HIV-infected children (<15 years old) initiating ART in 4 sub-Saharan HIV programs in Kenya, Uganda and Malawi, between December 2001 and December 2010. Rates of mortality, program attrition and first-line clinico-immunological failure were calculated by age group (<2, 2-4 and 5-14 years), 1 or 2 years after ART initiation and risk factors were examined.

Results

A total of 3,949 children, 22.7% aged <2 years, 32.2% 2-4 years, 45.1% aged 5-14 years, were included. At ART initiation 60.8% had clinical stage 3 or 4, and 46.5% severe immune-suppression. Overall mortality, attrition and 1-year failure rates were 5.1, 10.8 and 9.0 per 100 person-years, respectively. Immunosuppression, stage 3 or 4 and underweight were associated with increased rates of mortality, attrition and treatment failure. Adjusted estimates showed lower mortality hazard ratios (HR) among children aged 2-4 years (HR=0.57, 95%CI 0.42-0.77 compared to 5-14 years). One-year treatment failure incidence rate ratios (IRR) were similar regardless of age (IRR=0.91, 95%CI 0.67-1.25 for <2 years; 1.01, 95%CI 0.83-1.23 for 2-4 years, compared to 5-14 years).

Conclusions

Good treatment outcomes were achieved during the first decade of HIV pediatric care despite the late start of therapy. Encouraging early HIV infant diagnosis in and outside prevention of mother-to-child-transmission programs, and linkage to care services for early ART initiation are needed to reduce mortality and delay treatment failure.

INTRODUCTION

Only 32% of HIV-positive children in need of antiretroviral therapy (ART) actually receive it, compared to 41% of adults in 2014 (1). National HIV programs and health providers in resource-limited countries face important challenges. Access to HIV testing and care in rural and in deprived urban areas are particularly challenging and inequitable (2;3). Limited availability of trained staff, supervision and diagnostic tools, as well as drug stock ruptures and high costs associated with care provision, lead to delays in care access and suboptimal care quality. In 2013, the World Health Organization (WHO) recommended that children aged <5 years initiate ART immediately after diagnosis of HIV infection, and since 2015, ART-initiation upon diagnosis is recommended for children of all ages (4). Early pediatric diagnosis relies on virological testing, but its access and integration with prevention of mother-to-child transmission (PMTCT) services as well as non-PMTCT child health services remains limited in many resource-limited settings. In the absence of treatment, 53% of children will die before their second birthday (5), while late start of treatment is associated with poor treatment outcomes.

Once diagnosed and on treatment, children remain particularly vulnerable due to their dependence on adults to be diagnosed and to obtain adequate and regular treatment. Continuous family support is often lacking due to death or sickness of caregivers. Furthermore, the need to adjust drug doses to the changing weight of children (6) and lack of adequate pediatric formulations may lead to inadequate dosing (7), and ultimately increases the risk of virological failure and acquisition of drug resistance (7;8).

To evaluate the first 10 years of experience in treating pediatric HIV infection in four HIV programs in Malawi, Uganda and Kenya, we described the characteristics of children started on ART and compared age-specific patient outcomes after the first two years of ART start.

METHODS

HIV programs

In the early 2000's, Médecins Sans Frontières (MSF), in partnership with the Ministries of Health, started providing free medical HIV care in a non-governmental clinic of one of the urban slums of Nairobi (Kenya), in the regional referral hospital of Arua (Uganda), in a highly decentralized program in a rural district in Chiradzulu (Malawi) and in the rural district of Homa-Bay (Kenya). Cost-free medical services provided include HIV counseling and testing, PMTCT care, laboratory investigations, management of opportunistic infections, ART and hospitalization. Eligibility criteria for ART initiation are based on World Health Organization (WHO) recommendations for scaling-up

ART in low-resource settings. Children aged >18 months are diagnosed after obtaining two positive rapid antibody test results. Younger children are diagnosed through pro-viral DNA polymerase chain reaction tests performed on dried blood spots. Most children included in this analysis had received adult stavudine-based formulations. Pediatric fixed-dose combination drugs were provided after WHO prequalification (July 2007). Daily cotrimoxazole prophylaxis was prescribed.

Children were clinically examined at least monthly during the first 6 months of ART use, then every 2 to 3 months after clinical stabilization. Adherence counseling focused on parental/caregiver education, although initiatives to progressively involve children as they became older were gradually implemented. CD4 cell counts were measured before ART initiation and ever 6-12 months thereafter. No viral load monitoring was implemented but, since 2008, viral load testing was gradually introduced to confirm suspicion of clinical or immunological failure.

Data collection and study population

Data were prospectively collected and entered in the FUCHIA software (Epicentre, Paris, France) at each visit. Information collected included mode of entry (medical referral, voluntary counseling and testing, other), visit dates, sex, age, weight, height, WHO clinical stage, CD4 cell count and/or percentage, history of and prescription of antiretroviral drugs, and history of and current WHO clinical staging conditions, including tuberculosis.

Patients who started ART between December 2001 and December 2010 in one of the study sites, were aged <15 years at the date of treatment initiation, had more than one follow-up visit and had been registered 1 year or more before December 2011, were included in the analysis.

Study definitions

WHO standards for weight-for-age Z-scores were used, children underweight was defined as a weight-for-age score of <-2 in children of <5 years, or an age- and sex-specific body mass index (BMI) value equivalent to the <18.5 cut-off points for adults in 5-14 year old children (9;10). The nadir immunosuppression level was estimated as the lowest CD4 cell percentage (age <2) or count (age 2-14) (11), among measurements recorded within 3 months before and 12 months after ART initiation. Nadir immunosuppression was classified as severe (CD4 percent <15% or count <200 cells/µL), moderate (CD4 percent of 15-24% or count of 200-350 cells/µL); or absent (CD4 percent >25% or count of >350 cells/µL).

Children with history of PMTCT drug use were those whose mothers had recorded use of PMTCT prophylaxis during pregnancy/labor/delivery and/or those who had recorded prescription of PMTCT prophylaxis after birth.

For each patient, first-line treatment failure was defined as the earliest clinical, immunological or virological failure event (12). Clinical failure was a recorded diagnosis of a recurrent or a new WHO clinical stage 3 or 4 condition after 6 months of first-line use. Immunological failure was defined as a decline in CD4 cell count or percentage to baseline value or below; a decline of ≥50% from the highest on-treatment measurement after 6 months of therapy, in CD4 cell count or percentage; or a CD4 cell count below 100 cells/µL after 1 year of therapy. Virological failure was a plasma HIV viral load value of more than 5000 copies/mL after 6 months of ART.

The dates of follow-up appointments for each patient enrolled in the HIV clinics are recorded in the electronic health record system of the programs. For patients receiving ART, these appointments are generally scheduled monthly. For the purpose of the study, a child was considered lost to follow-up (LTFU) if the last scheduled appointment was missed for ≥2 months or, when no date of next appointment was specified, if he/she did not attend the clinic for ≥6 months. Attrition was defined as a composite endpoint of death or LTFU. Children who attended <5% of their appointments with delay were considered 95% or more adherent, those with 5% to 9% of delayed appointments were considered 90% to 94% adherent, and those with 10% or more delayed appointments were considered <90% adherent to therapy (13;14).

Statistical analysis

Patient characteristics at ART initiation were described by age group (<2, 2-4 and 5-14 years) and by period of treatment start. For longitudinal analyses, patient follow-up was right-censored at the earliest of the following dates: event (death or failure diagnosis), last clinic visit (for patients LTFU), transfer outside the program, or 1 year after ART start for children aged <2 years old and 2 years after ART start for children ≥2 years old for non-FTFU patients. Rates of mortality, attrition and first line failure were calculated as number of events per 100 person-years of follow-up.

Risk factor analyses were performed using adjusted Cox proportional hazard models (mortality) and Poisson regression (attrition and treatment failure). Factors considered for adjustment included: study site, mode of entry and sex; age group, clinical stage, underweight (binary indicator), and tuberculosis diagnosis at ART start; year of ART initiation (2001-2004, 2005-2007 and 2008-2010), nadir immunosuppression level and adherence index. For the attrition analysis, temporal changes in attrition rates after the start of ART were studied after splitting patient follow-up into ≤3, 4-6 and 7-24 months. Final models were adjusted for baseline characteristics associated with the outcomes in univariable analyses (P<0.2) and for gender and study site. Missing covariate data were included as a separate category. The fit of the final models was assessed with the goodness-of-fit test.

A sensitivity analysis was performed including only patients with complete case data. All analyses were performed with Stata 11 (Stata Corp, USA).

RESULTS

Patient characteristics

The 3,949 HIV-infected children who initiated ART between December 2001 and December 2010, and had more than one medical visit recorded were included (Figure 1). Fifty percent of children were females, 897 (22.7%) were aged <2 years and 1,780 (45.1%) aged ≥5 years at ART initiation (Table 1). The median age was 4.2 years (IQR 2.1-8.2). The number of children who started treatment doubled between the 2001-2004 and 2005-2007 periods. While the number of initiations slightly declined for children of ≥2 years after 2007, they continued to increase for the younger group (from 337 in 2005-2007 to 504 in 2008-2010). The median age at ART initiation decreased over time, from six years (IQR 3.5-9.3.) in 2001-2004 to three (IQR 1.6-8.1) in 2008-2010 (Table S1). Baseline characteristics were generally similar across the three age groups. The primary modes of entry in the program were through voluntary counselling and testing services (48.0%) and medical referral (41.7%). At ART initiation, 60.8% of patients were in clinical stage 3 or 4, 1,655 (46.5%) were severely immunosuppressed, 1,660 (44.3%) were underweight and 630 (16.0%) had been diagnosed with tuberculosis. A total of 3,798 (96%) had no recorded prior history of PMTCT drug use. The median time between program entry and ART initiation was 2.6 months [IQR 1.0-7.6] and did not differ by age. Almost all patients received a combination of two nucleoside reverse transcriptase inhibitor (NRTI) and one non-NRTI (NNRTI) drugs (n=3861, 97.8%). Children starting ART in 2001-2004 were more likely to be diagnosed with tuberculosis, compared to those starting in 2005-2010 (Table S2). At ART initiation, in 2001-2004, 103 (17.1%) were clinical stage 1 or 2 compared to 1335 (40.8%) in 2005-2010.

Mortality and program attrition by age group

During the 5,858 person-years of follow-up, 299 (7.6%) children died and 337 (8.5%) were lost to follow-up. The median time between ART initiation and death was 6.5 months (IQR 2.0-15.9) and it was higher for the 2-4 year group than for other age groups (8.5 months, IQR=2.0-29.1; compared to 7.0 months, IQR=2.3-15.4 among <2 year olds, and 5.3 months IQR=1.9-12.3 in the 5-14 year group). The overall mortality rate was 5.1 (95%CI 4.6-5.7) per 100 person-years and was 1.1 per 100 person-years (95%CI 0.7-1.6) in the second year of ART use. Mortality decreased over time from 14.3 per 100 person-years (95%CI 12.1-16.9) during the first three months of therapy to 2.6 per 100 person-years (95%CI 2.1-3.2) after 6 months of ART use (Figures 2 and table 2).

The overall attrition rate was 10.8 (95%CI 10.0-11.7) per 100 person-years and, as for mortality, attrition declined from 25.4 per 100 person-years (95%CI 22.4-28.8) during the first three months of therapy to 6.8 per 100 person years (95%CI 6.1-7.7) after 6 months of ART use (Table 2).

Crude rates of mortality were higher among the youngest children (12.1 per 100 person-years, 95%CI 9.9-14.9, compared to 2.9 per 100 person-years, 95%CI 2.3-3.7, in the 2-4 year group and 4.8 per 100 person-years, 95%CI 4.1-5.7, in the 5-14 year group; Table 2). Indeed, adjusted estimates showed lower mortality HRs for children aged 2-4 years (HR=0.57, 95%CI 0.42-0.77 compared to the eldest group). Similarly, higher crude attrition rates were observed in children aged <2 years than in older children (22.8 per 100 person-years, 95%CI 19.7-26.5, compared to 8.7 per 100 person-years, 95%CI 7.6-10.1, in the 2-4 year group and 9.3 per 100 person-years, 95%CI 8.2-10.4, in the 5-14 group). However, no significant age differences were found after adjustment for baseline covariates (incidence rate ratio [IRR]=1.20, 95%CI 0.97-1.48 for <2 years and IRR=0.88, 95%CI 0.72-1.06 for 2-4 years, compared to the 5-14 year group).

Risk factors for mortality and program attrition

Presence of severe immunosuppression (HR=2.69, 95%CI 1.77-4.10), underweight (HR=2.02, 95%CI 1.57-2.61) and advanced clinical disease (HR=1.58, 95%CI 1.11-2.24 for stage 4 compared to stages 1 or 2) were all factors associated with increased mortality (Table 2). Children diagnosed with tuberculosis had also increased mortality (HR=1.43, 95%CI 1.06-1.91). The same associations were identified when complete case analyses were performed. The exception was clinical stage 4, which was no longer significantly associated with increased mortality in the complete case analysis. Furthermore, estimates for the calendar year period of ART initiation were inconsistent, with higher mortality hazards being observed for children who started therapy during the earliest period (2001-2004 vs. 2008-2010) in complete case analyses.

Program attrition was also more common in children with severe clinical disease (IRR=1.65, 95% CI 1.30-2.09 for stage 4 compared to stages 1 or 2); underweight (IRR=1.65, 95%CI 1.40-1.95) and moderate and severe immunosuppression (IRR=1.57, 95% CI 1.17-2.10 and IRR=1.87, 95% CI 1.44-2.44, respectively, compared to absence of immunosuppression). It was also higher during the first 3 months of follow-up (IRR=2.49, 95% CI 2.08-2.99 for 0-3 months; and IRR=1.51, 95%CI 1.21-1.88 for 4-6 months, compared to 7-24 months post-ART initiation). Complete case analyses identified the same risk factors (Table 2).

Treatment failure by age group

During the study period, children contributed 5369 person-years of follow-up to the treatment failure analysis and 484 (12.2%) children were diagnosed with ART failure. The median time between ART start and failure diagnosis was 10.7 months (IQR 8.1-14.6). It was 8.1 months (IQR 7.3-10.2)

in children aged <2 years, 11.1 months (IQR 8.2-14.2) in those aged 2-4 years, and 11.4 months (IQR 8.3-15.6) in the 5-14 group. Rates of failure did not differ by age (IRR=0.91, 95%CI 0.67-1.25 in the youngest children; and IRR=1.01, 95%CI 0.83-1.23 in the middle age group, compared to the 5-14 year group). During the 6-12 month period failure rates were lowerin the younger group but differences were not statistically significant (14.9 vs. 20.1 and 18.8 per 100 person-years, respectively; Figure 2C). Rates decreased over time to 8.6 per 100 years (95%CI 6.9-10.9) in the 12-24 month period for children aged 2-4 years; and to 9.8 per 100 person-years (95%CI 8.2-11.8) in 5-14 year olds.

Risk factors for treatment failure

Female patients were less frequently diagnosed with treatment failure than males (IRR=0.75, 95%CI 0.62-0.89; Table 3). In contrast, increased proportion of failure was observed in children starting ART with advanced clinical disease (IRR=1.37, 95%CI 1.04-1.80 for stage 4 compared to stages 1 or 2), underweight (IRR=1.35, 95%CI 1.12-1.63) and severe nadir immunosuppression (IRR=1.67, 95%CI 1.33-2.11). Patients with lower adherence index (higher proportion of missed visits over the time of follow-up) were also more likely to be diagnosed with failure (IRR=1.69, 95%CI 1.27-2.24 for <80% compared to ≥95% adherence). Furthermore higher IRRs were also observed among children who started ART in the earlier calendar period (IRR=1.64, 95% CI 1.26-2.12 compared to 2008-2010). Analysis restricted to patients with complete case data identified the same associations, except for females for whom this relationship was no longer significant.

DISCUSSION

In this study we report patient characteristics and good treatment outcomes of a large cohort of children infected with HIV who started therapy during the first decade of pediatric ART provision in four HIV programs in Kenya, Uganda and Malawi.

Overall, children started ART late and many with advanced clinical disease. However, the median age at ART start decreased by half over time (from six years in 2001-2004 to three in 2008-2010) and the percentages of children with advanced clinical stage and with tuberculosis gradually lowered. A decline in age and in prevalence of severe HIV disease at ART initiation has also been recently reported among 30,000 children in four sub-Saharan countries during the period 2005-2010 (16). One reason for these changes is likely related to changes in the WHO recommendations for pediatric care, which recommended ART “as soon as signs of advanced HIV disease developed” (17;18). With increasing evidence of the benefit of early ART initiation in infancy (19-21), guidelines were updated to recommend therapy immediately after HIV diagnosis, regardless of clinical and immunological status to younger age children (in 2010 for children between one and two years (11), in 2013 to children below five (22), and since 2015 to all independent of age (4). Another key factor contributing to delayed pediatric ART initiation is the

limited or lack of access to virological testing for early infant diagnosis in- and outside PMTCT programs (for example in malnutrition wards (23;24)). By the end of 2013, the estimated percentage of HIV-exposed infants who benefited from virological testing within two months of birth was only 42% in Kenya, 36% in Uganda and 15% in Malawi (24).

Despite late start of treatment, 2-year mortality rates (5.1 per 100 person-years) were good and similar to estimates reported in other sub-Saharan African and South-East Asian programs (25-33). Lower death rates have been reported in Thailand (1.3 deaths /100 person years) (34), and higher estimates in rural Mozambique, where 39% lost-to-follow-up and 29 % death after 2 years on ART were reported among 735 children (35). Comparisons of mortality across settings are however problematic, due to disparities in undocumented deaths. In a study conducted in our program of Chiradzulu, half of the children initiated on ART and LTFU had died (36), and in our study LTFU and death rates were of similar size, resulting in an attrition rate of 10.8 per 100 person-years.

In agreement with other studies (25;26;28;30;33;37;38), we found an increased risk of death and attrition in children with advanced HIV disease (defined by clinical stage, immune-suppression, tuberculosis or underweight). Irrespective of age at therapy start, failure estimates were highest within the first 3 months post-ART, highlighting the need for close monitoring during this critical stage. Some studies identified young age at ART start (younger than 6-18 months) as a risk factor for mortality (30;32;37-42). In our analysis, crude mortality was four times higher amongst children of <2 years, and about twice as high in 2-4 year olds compared to the older group. However, in adjusted analyses the lowest mortality was observed in the 2-4 year group. This might result from a combination of the early death of vulnerable younger undiagnosed children (43), an increasing risk associated with longer exposure to HIV in older surviving children who did not benefit from adequate PMTCT prophylaxis and were diagnosed late in the course of HIV infection, and the difficulties to maintain good treatment adherence in the eldest children, which depends on full disclosure status, acceptance of the disease and a supporting environment during the adolescent period.

About one of eight children (12.2%) met treatment failure criteria during follow-up and no age-differences in rates were observed. However, rates are likely to have been underestimated, since failure was essentially defined by immunological and clinical criteria, which are known to be inaccurate (44-47), and viral load testing was only available for a small proportion of children. Previously reported 2-3 year virological failure rates in pediatric populations range from 14% in Cambodia (48) to 38% in rural South Africa (8); and a meta-analysis of studies conducted in resource-limited settings reported a pooled virological failure estimate of 30% after 1 year of ART among <18 year olds (49). Current efforts to roll-out access to routine viral load monitoring are expected to improve timely detection of pediatric ART failure (50), and to permit a more accurate evaluation of the effectiveness of pediatric treatment programs.

In our analysis, treatment failure was more frequent in children with advanced HIV disease and during the first 6-12 months of treatment, emphasizing the importance of early ART initiation, careful monitoring and adherence support during the first months of treatment. Children who started ART in later periods (2008-2010) had lower failure rates, which are likely related to improvements in clinical management and access to pediatric formulations over time.

In the present study, many children were initially underweight and had a higher risk of mortality, lost-to-follow-up and treatment failure. Underweight and/or malnutrition are known risk factors of mortality in HIV-infected children (25;26;33;51;52); and systematic initial and regular monitoring of nutrition status at ART initiation is recommended (22). Tuberculosis represents another serious threat for HIV-infected children, and is an important cause of death (53;54). Unfortunately, pediatric tuberculosis diagnosis is challenging, largely based on clinical symptoms and often presumptive. The percentage of children with tuberculosis at ART start in our study is therefore likely to be underestimated. Nevertheless we found clear evidence of increased mortality in children with tuberculosis. Systematic screening for tuberculosis and timely start of prophylaxis, treatment are also important to prevent pediatric deaths.

This study provides real-world estimates of treatment outcomes achieved during the first decade of pediatric ART provision under programmatic conditions in four large MSF-supported HIV programs in sub-Saharan Africa. It included nearly 4,000 children of different age groups with a balanced sex distribution. Besides the limitations already discussed, it is important to note that the risk factor analysis could only consider patient characteristics and clinical data routinely collected for patient care and program monitoring in the HIV registry. No information was available on reason for LTFU or the proportion of deaths amongst children LTFU and analyses were not adjusted for characteristics of health facilities. Furthermore, our data were limited to 2 years of pediatric ART follow-up. Analysis and reporting of longer-term outcomes, especially for infants who have benefited from greater access to early infant diagnosis and diagnostic tools and to treatment with pediatric ART formulations in recent years, are therefore needed.

Conclusion

Despite late presentation and relatively advanced age at ART start, the good pediatric outcomes observed after 1-2 years of ART use, demonstrate that pediatric ART provision can be feasible and effective in resource-limited settings. Our findings indicate that early ART start, before signs of clinico-immunological deterioration appear might be beneficial for children of all age groups and that close monitoring during the first months of therapy is critical to improve pediatric care.

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