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TRENDS IN ADVANCED HIV DISEASE AND LONG-TERM OUTCOMES OF HIVINFECTED CHILDREN TREATED WITH ANTIRETROVIRAL THERAPY IN EASTERN AND SOUTHERN AFRICA: 2003-2017

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DEDICATION

To my parents Andronica and Joseph Elyanu

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Summary

Despite the over 10-years' experience providing pediatric antiretroviral therapy(ART) and implementing different WHO guidelines, data on updated trends (after 2010) in advanced disease at ART start, and on long-term survival of children receiving ART are scarce. Without these data, the impact of recent WHO guidelines on early treatment initiation and long-term survival remains unclear. First, we examined trends in advanced disease at ART start, then described 10-year survival and investigated risk factors of early mortality in children treated with ART and lastly examined the association between rapid ART initiation and outcomes (mortality and loss to follow-up) of HIV infected.

We studied children (0-14 years) with HIV who initiated ART at seven Baylor International Pediatric AIDS initiative supported clinics in Botswana, Lesotho, Malawi, Swaziland, Tanzania, and Uganda. For the first aim, we conducted a pooled cross sectional study of children (N=20,605) who initiated ART between 2003 and 2017. We examined the linear trends in the proportion of children with advanced disease (over seven periods of ART initiation

corresponding to WHO guideline implementation period) using the Cochran-Armitage test for trend. For the second aim, we conducted a retrospective cohort study of children (N=18,010) who initiated ART between 2003 and 2017. We estimated 10-year survival using the Kaplan-Meier approach and assessed risk factors of early mortality using Cox proportional hazard regression. For the third aim, we conducted a retrospective cohort study of children (N=3,299) who initiated ART between 2014 and 2017. We examined the association between rapid ART initiation and outcomes of children using sub-distribution hazard regression for competing risks, treating death and loss to follow-up as competing risks.

Between 2003-2017, the proportion of children initiating ART with advanced disease declined among ages 5-9 years (58.3% to 39.9%; p<0.01) and 10-14 years (61.9% to 38.1%; p<0.01), remained the same for ages <2 years (72.7% to 70.6%; p=0.1), and increased for ages 2-4 years (59.4% to 62.3%; p<0.01). 10-year survival probability %(95%CI) was 88.9 (88.3-89.5) overall, 83.7 (82.5-84.8) in children aged <2 years, 91.9 (90.7-93.0) in those 2-4 years, 92.6 (91.5-93.6) in 5-9 years and 88.8 (9 87.2-90.2) in 10-14 years. Half of the deaths occurred within 6–months of therapy. The risk factors of mortality were: baseline age <2 years (aHR 1.41(95% CI: 1.11-1.79) compared to 10-14 years; WHO stage 4 (aHR 2.95(95% CI 2.33-2.72) and stage 3 (aHR 1.36(95% CI: 1.06-1.73) compared to stage 1 and 2 disease; severe (aHR=6.71, 95% CI 5.29-8.52) and moderate (aHR=2.64, 95% CI 1.90-3.66) immune suppression compared to no/mild immune suppression; and severe underweight (aHR 1.84 (95% CI 1.48-2.29) compared to normal weight-for-age. The risk of mortality was similar between children who initiated ART on the same-day [adjusted sub distributional hazard risk (aSHR) =1.10, 95% CI 0.79, 1.75] and those who initiated within 2-7 days (aSHR=1.05, 95% CI 0.77, 1.43) compared to those who initiated within 8-90 days. The risk of LTFU was higher in children who initiated ART on the

same day (aSHR=1.86, 95% CI 1.39, 2.49) and those who initiated within 2-7 days (aSHR=1.83, 95% CI 1.38, 2.43) compared to those who initiated within 8-90 days.

The proportion of children with HIV aged 5-14 years who initiate ART with advanced disease has reduced, and long-term survival in those treated with ART is good. However, nearly two-thirds of children aged <5 years are still initiating ART with advanced disease, early mortality is high, and disease severity characteristics were associated with a higher risk of early mortality. A significant proportion of those who initiate ART rapidly is lost to follow-up. While programs can use the good survival outcome to motivate caretaker to test and initiate ART early in children, more work is required to diagnose, initiate and keep children with HIV in care.

TABLE OF CONTENTS

LIST OF TABLES

Journal article 1

Journal article 2

Journal article 3

LIST OF FIGURES

Journal article 1

Journal article 2

Journal article 3

BACKGROUND

INTRODUCTION

For nearly one and a half decades, combination antiretroviral therapy (ART) has been the standard approach for treating pediatric HIV in the Eastern and Southern Africa region (ESA), and it has improved short-term outcomes of HIV-infected children [1-4]. Since the introduction of ART, ESA countries have followed the World Health Organization (WHO) guidelines to provide ART to HIV infected children. The WHO guidelines have continually changed to recommend treating HIV infected children at a younger age, with less severe HIV disease, and with more-effective first-line ART [5-9]. These changes mean that over time children who start ART should be younger, have less advanced disease and have better survival. Reports have shown declining trends (up to 2010) in median age and proportion of children with advanced HIV disease [10-15]. Additionally, cohort studies have shown 1-2 year survival probability after ART of 80-90% [3, 4], and losses to follow ranging from 2-39% [16, 17]

Pediatric HIV treatment in resource-limited settings, however, continues to face challenges, which can affect early HIV diagnosis in children and long-term outcomes (survival and LTFU) of HIV infected children. These include limited access to virological tests for early infant diagnosis and the continued need to adjust treatment ART doses as the child's weight increases. Moreover, children depend on caregivers to administer their medicines, and when they become adolescents, they may not adhere to ART because of non-disclosure or treatment fatigue. Poor adherence to ART could lead to treatment failure, disease progression, and death. Despite these challenges of providing pediatric ART and the over 10-years' experience providing pediatric ART and implementing different WHO guidelines, data on updated trends (after 2010) in baseline line characteristics, and on long-term survival and LTFU of children initiating ART

are scarce. Without updated trends in baseline characteristics of children at ART initiation, the impact of recent WHO guidelines on early treatment initiation remains unclear. Additionally, not knowing long-term survival and LTFU of children on ART precludes our understanding of the impact of ART programs on long-term survival in HIV infected children.

Our study aimed to examine temporal changes in baseline characteristics and to investigate predictors and rates of long-term survival and loss to follow-up of HIV infected children who start ART.

LITERATURE REVIEW

The Burden of pediatric HIV in Eastern and Southern Africa is high.

ESA carries the highest burden of total HIV infections, new HIV infections and HIV-related morality in the world. In 2017, an estimated 66% (1.2 million of 1.8 million) of children living with HIV worldwide were in ESA[18, 19]. Additionally, 51% (92,000 of 180,000) of new pediatric infections were in ESA. The region has made significant progress identifying and initiating HIV infected children on ART with currently 59% of children receiving ART compared to a 52% global average [19]. However, 47% (52,000 of 110,000) of all global pediatric HIV deaths are in ESA and HIV is among the top 10 causes of death among children in this region [20]. In order to decrease pediatric HIV deaths, the ESA countries have adapted and implemented the WHO pediatric HIV treatment guidelines.

Changes in the WHO guidelines for treating HIV infected children.

WHO HIV treatment guidelines consist of criteria of when to initiate ART in HIV infected children and what ARV regimen to use. Since 2004, WHO has released five sets of guidelines for treating HIV in children, each providing more simplified criteria than the one

before (table 1). These guidelines have progressively recommended treating HIV-infected children with less advanced disease, at a younger age, and with more effective first-line ART.

The first guidelines, released in 2004, provided WHO clinical stage criteria and age-specific immunological (CD4 cell count/percent) thresholds for starting ART in HIV infected child (table 1). The second set of guidelines, released in 2006, recommended higher CD4 thresholds for starting ART than those in 2004. For example, the 2006 guidelines recommended initiating ART in children aged <1 year at a CD4 threshold of <25% compared <20% in 2003. The higher the CD4 count or percent, the less severe the disease is.

In 2010, after the children with HIV early antiretroviral (CHER) trial showed that early HIV diagnosis and early ART reduced infant mortality by 76% and HIV progression by 75% [21], WHO released a third set of guidelines. These guidelines recommended immediate ART for all HIV infected children aged <2 years irrespective of WHO clinical stage or CD4 count and a higher CD4 threshold for older children [6].

In 2013, the WHO then released the fourth set of guidelines recommending immediate ART for all children aged <5yrs and again higher CD4 counts for older children [8]. In 2015, WHO dropped the clinical and immunological criteria and recommended immediate ART for all children aged <15years irrespective of WHO clinical stage or CD4 cell count [9]. Each set of guidelines included treatment regimens as shown in table1. The changes in criteria for initiating children on ART should be reflected in the baseline characteristics of children who initiate ART. Additionally, in 2017, WHO recommended rapid ART initiation (initiating ART within seven days upon diagnosis) in all people living with HIV including children.

Table 1: Summary of the changes in WHO guidelines on when to initiate ART and the First-line ARV medicine

<table>
<tr><th>Guideline</th><th>Age</th><th>2003</th><th>2006</th><th>2010</th><th>2013</th><th>2015</th><th>2017</th></tr>
<tr><td rowspan="7">Criteria for initiating ART*</td><td><12 months</td><td rowspan="2">CD4 <20%</td><td>CD4<1500 or <25%</td><td rowspan="2">Treat all irrespective of CD4 or WHO stage</td><td rowspan="5">Treat all irrespective of CD4 or WHO stage</td><td rowspan="6">Treat all irrespective of CD4 or WHO stage</td><td rowspan="6">Rapid ART initiation (within one week) upon diagnosis and medical checks</td></tr>
<tr><td>12-18months</td><td rowspan="3">CD4<750 or <20%</td></tr>
<tr><td>18-24 month</td><td>CD4 <350 or <20%</td></tr>
<tr><td>24-35 month</td><td rowspan="2">CD4 <350 or <20%</td><td rowspan="2">CD4<750 or <25%</td></tr>
<tr><td>36-59 month</td><td>CD4 <350 or <15%</td></tr>
<tr><td>5-14 years</td><td>CD4 <200 or <15%</td><td>CD4 <200 or <15%</td><td>CD4 count <350</td><td>CD4<500</td></tr>
<tr><td rowspan="3">First Line ART regimen</td><td>NRTI 1</td><td>AZT or d4T</td><td>AZT or d4T or ABC</td><td>AZT or ABC or D4T</td><td colspan="2"><10yrs: ABC or AZT
≥10yr: TDF or AZT</td></tr>
<tr><td>NRTI 2</td><td colspan="5">3TC</td></tr>
<tr><td>Third ARV</td><td colspan="2">NVP or EFV
(EFV only if >3yrs and >10kg)</td><td><2 yrs; exposed to NVP: LPV/r
<2 yrs; not exposed to NVP: NVP
2-3 yrs: NVP
≥3yrs: NVP or EFV</td><td colspan="2"><3yrs: LPV/r
≥3 yrs: EFV</td></tr>
</table>

*For all the criteria, children with WHO clinical stage 3 or 4 HIV disease were eligible irrespective of age or CD4 cell criteria

Temporal trends in baseline characteristics of children at ART initiation.

Characteristics of children like age, WHO clinical stage, CD4 count and Weight for Age Z-score at diagnosis, entry into care and at ART initiation are measures indicating the duration of HIV disease. Characteristics at diagnosis and entry are a measure of early HIV diagnosis, while characteristics at ART initiation are a measure of early ART initiation. Early diagnosis and Early ART initiation mean children should be diagnosed and started on treatment at a young age and without advanced disease(WHO stage 1 or 2) or severe disease(CD4 count > 200 cells/mm^3). Early HIV diagnosis and Early ART initiation are critical to stop rapid disease progression in children and reduce mortality in HIV infected children. Measuring trends in these characteristics, therefore, provides a measure of progress towards early HIV diagnosis and early ART initiation in HIV-infected children, a major goal of the WHO guidelines. Studies have examined trends in baseline characteristics up to 2010, but the trends after 2010 are scarce.

Temporal trends in baseline characteristics of children starting ART up to 2010.

Up to 2010, there were decreasing trends in the median age and proportion of children with advanced HIV disease (WHO clinical stage 3 or 4) at ART start. However, a substantial proportion of children started ART when they were older or with advanced HIV disease. Moreover, the trends in the proportion of children who are underweight at ART start are inconclusive.

Studies that have examined trends in baseline characteristics of HIV infected children who started ART up to 2010 show decreasing median age and proportion of children with advanced HIV disease [10-15]. However, in 2009/2010 the median age at the start of ART was still high (range 3 -8 years) and half of the children started ART when they had advanced HIV

disease. Moreover, up to 80% of the children under five years of age had advanced HIV disease when they started ART [13].

In addition, studies that measured trends in the proportion of children who are underweight at ART start showed conflicting results. For example, a study using the International Epidemiology Databases to Evaluate AIDS (IeDEA) in five countries in Southern African showed a significant decrease in the proportion of children with moderate/severe underweight from 31% to 28% [13]. However, a study in South Africa [11], and another in three countries in East Africa [10] showed no change in the trend.

Young age, advanced HIV disease, and moderate or severe malnutrition are associated with higher mortality in HIV infected children [1, 3, 10, 22-26]. The trends in these baseline characteristics could have changed after 2010 because of the changes in WHO guidelines; however, data on the trends after 2010 are limited.

Data on temporal trends in baseline characteristics of HIV infected children starting ART beyond 2010 are limited.

Although most changes in WHO guidelines for treating HIV in children occurred after 2010, few studies examine temporal trends in baseline characteristics of HIV infected children initiating ART beyond 2010, and they show mixed results. For example, in the IeDEA cohort study of HIV infected children started on ART in three Central African countries (Burundi, Democratic Republic of Congo and Rwanda), the proportion of children with advanced HIV disease decreased from 55% in 2004/2005 to 42% in 2012/2013[12]. In contrast, in a cohort study in Tanzania, the proportion of children with advanced HIV disease increased from 46% in 2005/2007 to 76% in 2013/2014[27]. Moreover, while in the IeDEA cohort in Central Africa, the proportion of children with severe malnutrition decreased from 41% in 2004/2005 to 17% in 2002/2013[12], in another cohort study in Tanzania the proportion increased from 26% in 2008-

2012 to 62% in 2013/2014 [28]. Conversely, all three studies found a decreasing trend in the median age at ART initiation from 7yrs to 5.8 years in Central Africa, and 6yrs to 4 years in Tanzania [12, 27, 28].

These differences in the proportion of children with advanced disease and severe malnutrition may reflect variations in programmatic strategies in implementing guidelines. For example, in Tanzania, the program implemented active case finding in in-patient wards, which resulted in a higher yield of children with advanced disease. While in central Africa, there was expanded early infant diagnosis and the proportion of children identified with less advanced disease increased. Notably, in all of the above studies, the median age (4 -5.8yrs), and proportion of children with advanced disease (42-76%) or severe malnutrition (17-62%) in the last year of the study was high.

The inconclusive trends after 2010 highlight the need for more studies to examine updated trends in baseline characteristics of children starting ART. Knowing the updated trends improves our understanding of the impact of more recent WHO guidelines on early treatment initiation. Further, we can examine progress towards early diagnosis and early ART initiation. Early HIV diagnosis and early ART initiation reduce disease progression and mortality in HIV-infected children [21].

Survival among HIV infected children initiated on ART

Studies using routine ART program data in resource-limited settings (RLS) show variability in survival of HIV infected but most have short follow-up periods (1-2 years). However, data on long-term survival in RLS are scarce. Most data on long-term survival are from high-income countries, and most are cohorts of older children. Challenges of providing pediatric ART in high income and RLS differ. Therefore examining long-term survival and

predictors of mortality in RLS improves our understanding of the success of long-term ART in those settings and identifies opportunities for improvement.

Short-term survival of HIV infected children initiating ART

In RLS, cohorts studies using routine ART program report mortality of 4.3-29% [1, 11, 23, 29], mortality rates of 1- 6.9/100 person years [2, 10, 15, 22, 25, 30, 31], and survival probability of 90% in children on ART [4]. Most of these studies have follow up time of one-two years. The short follow-up time could be because the studies were earlier in the ART program before the children accrued longer follow-up time or by design. HIV, however, is a chronic disease and its treatment is life-long. In RLS, lifelong ART presents challenges that could affect the success of ART and long-term survival. For example, additional challenges in RLS may include that health care workers need to continually adjust treatment doses to the child's weight yet follow-up may be difficult/inconsistent, appropriate pediatric formulations may be lacking, there are high losses to follow-up, and there may be ARV stock-outs. Moreover, children are vulnerable because they depend on caregivers-who may be too sick to administer their medicines and as they grow into adolescents, they may not adhere to treatment because of non-disclosure of HIV status or treatment fatigue. All these challenges could lead to poor long-term adherence to ART, which can result in treatment failure, disease progression and death. Despite these challenges, data on long-term survival on ART in RLS are scarce.

Data on long-term survival of HIV infected children initiating ART in RLS are scarce

Studies examining long-term survival in HIV infected children receiving ART have mainly been from high and middle-income countries. These studies report 5-10 year mortality rate of 1.2-1.7 per 100 person-years and survival of >94-99% [32-36]. Few studies that report long-term mortality in RLS show 3-4 yr mortality of 3.6-7.7% among all children [3, 15] and 16% in infants [24], and survival of 81%[3]. More recent report show 8-years survival of 90% in

Mozambique [37] and about 89% in Zambia[38] .Most of the studies reporting long-term survival are among older children (median age 3.5-7 years). These studies do not examine age-specific long-term survival and yet long-term survival may differ by age because in studies with short-term follow-up, the risk of death is higher in younger children than older children [1, 3, 10, 22-26].

Given the challenges of long-term ART and the scarcity of data on long-term survival in HIV infected children and more so age-specific survival in RLS, there is a need to fill this knowledge gap. Examining long-term survival would improve our understanding of the success of long-term ART and identify opportunities for improvement.

Risk factors of mortality in HIV infected children receiving ART

Risk factors for death in HIV infected children receiving ART are well documented but risk factors of early and late death are not been described. Young age (<2yrs), advanced disease (WHO stage 3 and 4), severe immune suppression (CD4 <200 cell/mm^3 in children ≥5yrs or CD4percentage <15% in children <5yrs), severe malnutrition and TB disease have been associated with a high risk of death [1, 3, 10, 22-25, 30, 37]. However, most of these studies modeled the variables as fixed covariates and did not examine the risk factors of early (<6 months) and late mortality (≥ 6months) independently,yet, 50-60% of mortality in HIV infected children who initiate ART is within the first six months [30, 33, 39], and predictors of early (<6 months) and late mortality (≥6 months) may differ [33]. For example, a cohort study of HIV infected children receiving ART in Europe showed that although baseline age and advanced disease were risk factors for early death and not late death, time-updated BMI and severe immune suppression were risk factors for late death [33]. Examining predictors of late and early death in RLS is important because of the difference in infectious disease burden and quality of care between high-income countries and RLS.

Rapid ART initiation in children living with HIV

In 2014, the Joint United Nations Program on HIV/AIDS (UNAIDS) set ambitious targets described as "95-95-95" targets to end AIDS by 2030[40]. These targets are that 95% of people living with HIV know their HIV status, 95% of those diagnosed with HIV initiate and sustain ART and 95% of those on ART achieve and maintain viral suppression. To attain these targets, children diagnosed with HIV must be linked to HIV care, promptly initiated on ART and retained in care. However, 20% of children with HIV are lost to follow up between diagnosis and ART initiation [41]. After initiating ART mortality ranges from 4.3-29% [1, 11, 23, 29] and loss to follow-up(LTFU) ranges from 2-39% [10, 16, 17, 28, 29]. These high losses to follow-up and mortality if not addressed can preclude attainment of the 95-95-95 goals for children by 2035.

As a strategy to reduce loss to follow-up and mortality in people living with HIV, the World Health Organization in 2017 recommended initiating ART in all people with HIV within 7-days (including same-day initiation in people who are ready) upon diagnosis.[42]. This recommendation, also called rapid ART initiation, followed trial reports in adults showing rapid ART initiation was associated with an increased likelihood of starting ART, reduced mortality, and better viral suppression and retention in care as compared to delayed initiation [42-45].

Although the WHO recommended rapid ART initiation in children as well, data on the effect of rapid ART initiation on outcomes of children were limited and inconclusive. Two trial conducted among hospitalized children showed no difference in mortality in children who initiated ART rapidly versus those on delayed initiation[46], an observational study in Malawi showed improved outcomes in children with uncomplicated malnutrition [47]. None of these studies examine if rapid ART initiation is associated with loss to follow-up, Yet observational studies in adults show an increased risk of being lost to follow-up after rapid ART initiation compared to delayed ART initiation [48, 49]. Given the paucity of data on this topic in children,

further research is required to investigate the effect of rapid ART initiation on the outcomes of children.

PUBLIC HEALTH SIGNIFICANCE

This study will show trends in advanced in children starting ART in ESA over 15 years (2003-2017). Second, we will describe rates and predictors of long-term survival and report the association between rapid ART initiation and outcomes of children treated with ART. These outcomes will have a positive impact because they improve our understanding of how changes in the WHO guidelines over time have affected early treatment initiation and survival of HIV infected children. Further, this information could be used for health care planning and intervention development at clinic and government levels. For example, knowledge of predictors of mortality and LTFU will inform the development of interventions to improve survival and retention in care. Also, long-term survival rates could be used to model pediatric HIV epidemiological estimates and life expectancy in HIV infected children, and to guide patient decisions and patient education. Findings of the association between rapid ART initiation and outcomes of children may be used to inform future revisions of rapid ART initiation guidelines in children. Finally, these data provide a benchmark against which future intervention and guidelines will be measured.

SPECIFIC AIMS

Introduction of ART has led to a reduction in short-term mortality in children [1-4]. However, pediatric HIV diagnosis and treatment in RLS continues to be challenging because of limited access to virological tests for early infant diagnosis, the need for pediatric friendly ARV medicines and need for health care providers to continually adjust ARV doses to the child's weight. Even after starting ART, children continue to be vulnerable because they depend on

caregivers to administer their medicines, and when they become adolescents, they may not adhere to ART because of non-disclosure or treatment fatigue. Poor adherence to ART could lead to treatment failure, disease progression, and death, thus affecting long-term outcomes (survival and LTFU) in children. To improve outcomes of HIV infected children, WHO guidelines for treating children with HIV have changed over time to recommend treating HIV infected children at a younger age, with less severe HIV disease, and with more-effective first-line ART and more recently to initiate ART within seven days from diagnosis [5-9, 42]. These changes mean that over time children who start ART should be younger, have less advanced disease and have better survival.

Despite the challenges of providing pediatric ART, the over 10-years' experience providing pediatric ART and implementing different WHO guidelines, data on updated trends (after 2010) in baseline line characteristics, and on long-term survival and LTFU of children initiating ART are scarce. In addition, evidence of the effect of rapid ART initiation on outcomes of children with HIV is limited and inconclusive. Without updated trends in baseline characteristics of children at ART initiation, the impact of recent WHO guidelines on early treatment initiation remains unclear. Additionally, not knowing long-term survival and LTFU of children on ART precludes our understanding of the impact of ART programs on long-term survival in HIV infected children. Lastly, the lack of evidence of the impact of rapid ART initiation limits the uptake of this recommendation.

The overall objective, of this proposal, is therefore to examine trends in advanced HIV disease and to investigate predictors and incidence of mortality and LTFU children who start ART in ESA. The specific aims of this proposal are:

Aim 1: Examine trends in advanced HIV disease at ART initiation among children initiated on ART between 2003-2017 in ESA.

Hypothesis 1a: *we hypothesize that the proportion of children with advanced disease at ART initiation will reduce with an increasing calendar year of ART initiation.*

Aim 2: Investigate the incidence and predictors of all-cause mortality in HIV infected children starting ART during 2003-2017 in ESA.

2a. Investigate 10-year survival probability in HIV infected children initiating ART during 2006-2017 in ESA.

2b. Identify risk factors of early mortality in HIV infected children starting ART during 2006-2017 in ESA.

Aim 3: Investigate the association between rapid ART initiation and outcomes (mortality and loss to follow-up) of children with HIV who initiated ART between 2014 and 2017 in ESA

METHODS

STUDY SETTING

This study was conducted using data from the Baylor International Paediatric AIDS Initiative (BIPAI) network clinics in Botswana, Malawi, Swaziland, Lesotho, Tanzania, and Uganda. BIPAI, one of the first organizations to provide pediatric HIV care in Africa, started these network clinics in partnership with national governments [50]. The first clinics were started in 2003 in Botswana and Uganda. Other clinics were started in Malawi in 2004, in Lesotho and Swaziland 2005 and Tanzania in 2010. The HIV infected children in these clinics are treated following country-specific guidelines, which are adapted from WHO guidelines. These children have scheduled visits at least three monthly, and data at all clinics are recoded using the same electronic medical record (EMR) system. Altogether, these clinics have enrolled and initiated a cohort of over 30,000 HIV infected children on ART. This cohort of children provides an opportunity to examine trends in baseline characteristics and long-term outcomes of HIV infected children.

DATA COLLECTION

Individual patient data from routine clinic visits were pooled electronically de-identified and sent to the study team for cleaning. A data query was developed and used to extract the required variables (table 3). Extracted data was exported to a CSV file. New patient identifiers (ID) were assigned to each participant and unique identifiers removed. Only date of birth and date of enrolment in the clinic were maintained for computing time to event for data analyses. The BIPAI data administrator extracted and de-identified the data, retained the link between unique identifiers and new ID's and shared the data de-identified data with the research team for cleaning and analysis.

AIM SPECIFIC METHODS

Methods for specific aim 1:

Aim 1a: Examine trends in advanced HIV disease at ART initiation among children initiated on ART between 2003-2017 in ESA.

Study design

We conducted a pooled cross sectional study and trend analysis of baseline characteristics of cohorts of children who initiated ART between 2003 and 2017. The cohorts of children were grouped into seven calendar periods based on the year of ART initiation. The periods also correspond to the WHO guideline periods.

Study participants

We included all ART-naïve children with HIV aged <15 years who initiated ART between 1 January 2003 and 31 December 2017 at the COEs. Additionally, children exposed to antiretroviral prophylaxis for preventing mother to child HIV transmission were included.

Variables and definitions

The baseline variables at ART initiation included age, sex, weight, entry point to care, WHO clinical stage and CD4 count, CD4 percent, weight-for-age z-scores (WAZ). The entry points to care were the prevention of mother to child HIV transmission(PMTCT) clinic, inpatient ward/TB clinic(IPD/TB), outpatient department(OPD), voluntary counseling and testing(VCT), and referrals from other health facilities and outreaches(Others). WHO clinical stage and CD4 were considered to be "at ART initiation" if they were taken on or at a date closest to the ART initiation date within a window of 6-months before until 1-month after ART initiation. Weight were those taken ± 1months of ART initiation. WAZ for children aged < 10 years were computed using the WHO child growth standards [51, 52] and for children aged 10-14 years, the

Centers for Diseases control and prevention (CDC) growth standards were used[53]. The CDC growth standards were used for children ≥ 10 years because the WAZ scores were not available in the WHO child growth standards. Advanced HIV disease was defined as having WHO clinical stage III or IV disease and/or severe immune suppression for age (CD4% < 25% for children <1 year of age, <20% for children aged 1-3yrs, < 15% for children 3-5 years and <15% or CD4 count <200 cell/mm^3 for children aged 5-14 years)[42, 54].

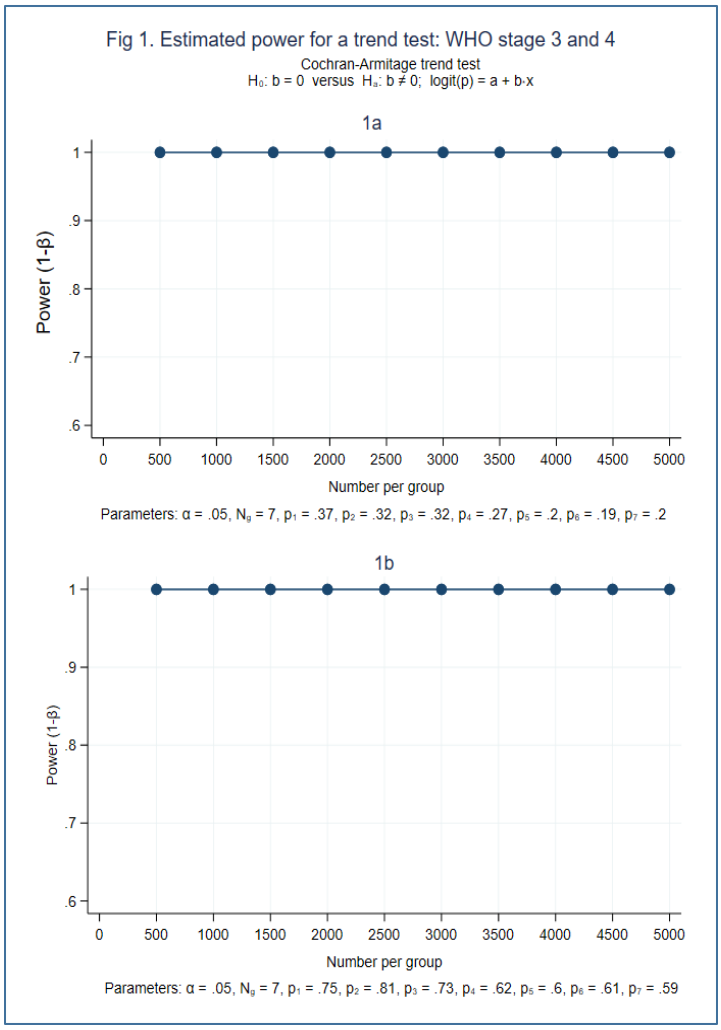
The years of ART initiation were grouped into seven calendar periods: 2003-2005, 2006-2007, 2008-2009, 2010-2011, 2012-2013, 2014-2015, and 2016-2017 as a proxy for when WHO guidelines were implemented. The period 2003-2005 is when the 2003 guidelines were implemented; 2006-2007 and 2008-2009 represent the 2006 guidelines period; 2010-2011 and 2012-2013 represent the 2010 guidelines period; 2014-2015 represents the 2013 guidelines period, and 2016-2017 represents the 2015 guidelines period.

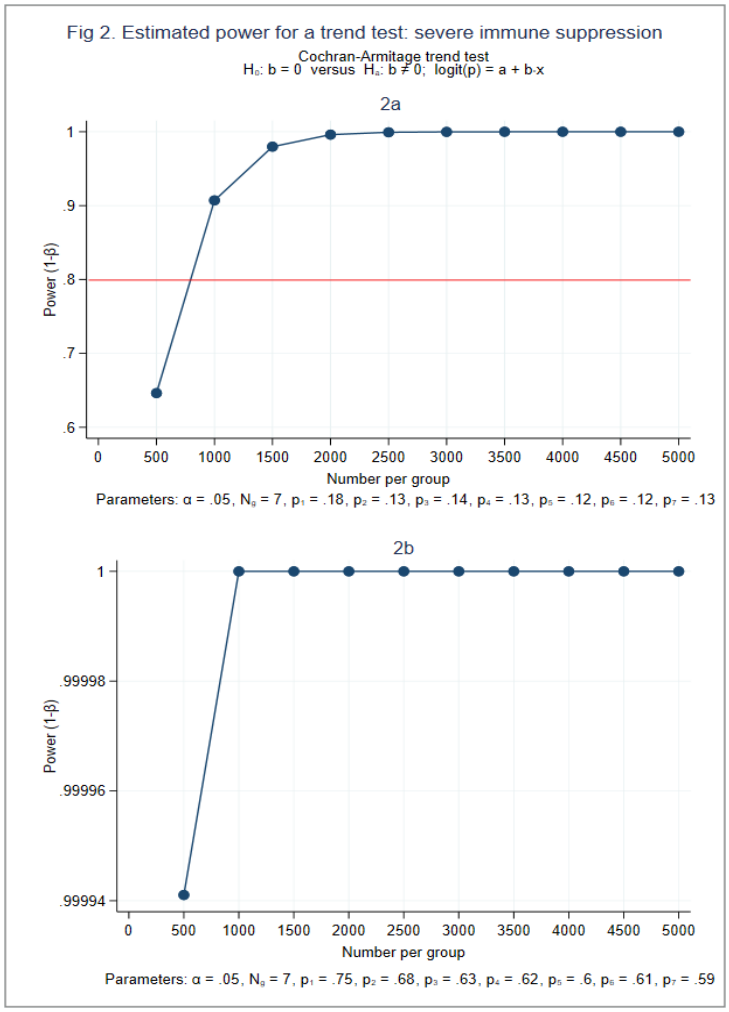
Power calculation

We estimated the power to detect a significant ($p<0.05$) linear trend in categorical variables using the Cochrane-Armitage trend test and trend in continuous variables using. The data categorized into seven groups corresponding to the period of enrolment in care and of ART initiation: 2003-2005, 2006-2007, 2008-2009, 2010-2011, 2012-2013, 2014-2015, 2016-2017. The total sample size is 25,000 HIV infected children, and the smallest group had 2000 HIV infected children. To estimate power, we used proportions and medians from previous trend studies from central Africa [12] and in southern African [13] and varied the sample size in each group between 500 and 5000. Power estimates from the proportions and medians from each study were plotted in separate graphs. The graphs plotted using the data from central African study were labeled (a) and those using the southern African study were labeled (b). A minimum sample

size of 800 in each group had 80% power to detect a significant linear trend in each variable (fig 2a). Since our data has at least 2000 children in each group, the study will have sufficient power to detect linear trends in all the baseline characteristics over time.

Figure 1: Estimated power for trend test for (a) the proportion with WHO stage 3 or 4 disease, (b) proportion with severe immune suppression





Data analysis

We summarized characteristics at ART initiations using medians (interquartile ranges [IQR]) and proportions for continuous and categorical variables respectively. The characteristics at ART initiation were analyzed by calendar period of ART initiation. Trends in categorical and continuous characteristics over the ordered calendar periods were assessed using the Cochran-Armitage test and Cuzick's test for trend respectively. We examined overall trends in advanced disease as well as by age-specific (<2 years, 2-4 years, 5-9 years and 10-14 yrs.) and country-specific trends.

Methods for specific aim 2

Aim 2: To investigate the incidence and predictors of all-cause mortality in HIV infected children starting ART during 2003-2017 in ESA.

Study design, and population

This was a retrospective cohort study using patient-level data pooled from seven BIPAI COEs in Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda. We included children with HIV aged <15 years who initiated ART between January 2006 and June 2017 and had two or more follow-up visits after ART initiation. Children who were ARV experienced (except for exposure to ARVs for PMTCT) at entry into care were excluded. The cohort start date for Tanzania was 2010, corresponding to the period when the clinic became operational.

Study variables and definitions

The independent study variables were age, sex, country, weight, height, WHO clinical stage, CD4 count, CD4 percent, weight for age Z-scores (WAZ), BMI for age Z scores (BAZ), ART regimens, TB diagnosis, hemoglobin levels(Hb) and immune suppression level. The child's weight or height was considered to be at ART start if they were taken ± 1month from the ART

start date, while WHO stage and CD4 count or percent at ART start were taken on or at a date closest to the ART initiation date within six months before and one month after ART initiation. We computed the WAZ for children aged < 10 years and BAZ for all children using the WHO child growth standards [51, 52]. WAZ for children aged 10-14 years using the Centers for Diseases Control and Prevention (CDC) growth standards [53] because this measure was not available for the age group in the WHO growth standards. CD4 counts or CD4 percentage were categorized into immune suppression levels (no/mild, moderate or severe) for age according to the WHO classification [42, 54]. The calendar period of ART initiation was categorized into three, 4-year periods: 2006-2009, 2010-2013 and 2014-2017 corresponding to WHO guideline periods; 2014-2017 covered two guideline periods.

The main outcome variable was all-cause mortality and was defined as death from any cause including HIV related and non-HIV related deaths. The date of death was extracted from the EMR. If the date was missing, we used the date the chart was closed. Other events that were censored in the analysis were lost to follow-up (LTFU), transfer out and active in care. The patient was considered LTFU if there was a gap of 90 days between their next clinic appointment and the database closure date (December 31, 2017). The date of LTFU was the chart closure date, and if the chart was not closed, the patient was censored 90 days after the last scheduled appointment. The patient was considered transferred-out if the transfer was documented and the date of transfer was that recorded in the chart.

Statistical analysis

Patient characteristics at ART initiation were described using summary statistics (medians and proportions) by age groups (<2 years, 2-4 years, 5-9 years and 10-14 years). We computed overall mortality rates per 100 person-years (PY) and rates within the first six months

of ART, at 6-24 months and after 24 months. Kaplan-Meier estimates for 10-year survival probability was calculated overall, by age group, country, and calendar period of ART initiation; differences in survival curves were tested using the log-rank test. Time to death was computed from the date of ART initiation, and children were right-censored at the earliest of either LTFU, transfer out, 10-years of follow-up or database closure date. We examined risk factors of mortality in the first 6-months and 6-24 months on ART using univariable and multivariable Cox proportional hazard regression models. We limited the analysis to the first 24 months to enable us to examine the effect of the most recent WHO- treatment guidelines (2014-2017) on survival. We used a stepwise regression method to select the most parsimonious model. The criteria for a variable to enter and to stay in the model were $p \leq 0.15$ and $p \leq 0.05$, respectively. Known predictors of death, including WHO clinical stage, immune suppression level, and age were purposefully included in the analysis. We tested the proportional hazards assumption using the Schoenfield test. To avoid loss of information and biased estimates because of missing data, we imputed missing CD4, WHO stage, WAZ, and Hb values using multiple imputation by chained equations (MICE), using 20 cycles[55, 56]. We conducted sensitivity analyses using complete case analysis and competing risks analyses with LTFU as the competing risk.

Methods for Specific Aim 3

Aim 3: Investigate the association between rapid ART initiation and outcomes (mortality and loss to follow-up) of children with HIV who initiated ART between 2014 and 2017 in ESA.

Study design

We conducted a retrospective cohort study using electronic medical records of children with HIV who initiated ART at seven BIPAI COEs in Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda.

Study participants

We included ART_naive HIV-infected children aged <15 years who entered HIV care at the study sites between January 2014 and 2017, and initiated ART within 90 days of enrolment. The 90 days was the median time to ART initiation observed among patients diagnosed at enrolment in a global study of access to ART in children [41]. However, we also assumed that if children were eligible at enrolment, ART should be initiated at most within 90-days. We excluded children who initiated ART less than 6-months from the database closure date (December 31, 2017).

Variables and definitions

Exposure: The exposure was rapid ART initiation, which we defined as initiating ART within 7-days of enrollment into care [42]. We categorized rapid initiation into same-day initiation and initiation within 2-7 days. The comparison group was those who initiated ART within 8-90 days (delayed initiation).

Outcome: The outcomes of the study, were all-cause mortality and LTFU. LTFU, defined as having a gap of 90 days between the next clinic appointment and the database closure date (December 31, 2017). The date of LTFU was the chart closure date, and if the chart was not closed, the patient was censored 90 days after the last scheduled appointment. The other outcomes were death, transfer out and active in care. The date of death and of transfer out were the dates recorded in the EMR, and if missing, the chat closure date was used. Children were considered active in care if none of the other outcomes had occurred and they were assigned the date of the last visit as the outcome date.

Other covariates: Other covariates considered were age, sex, country World Bank income category(middle income vs. low income), weight for age Z-scores (WAZ), TB diagnosis, WHO clinical disease stage (WHO stage) and immune suppression level and period of initiation(2014-2015 versus 2015-2016). The WAZ was computed from the weight taken on the ART start date. If weights were missing, weight taken ± 1month from ART start date was used. WAZ for children aged < 10 years were computed using the WHO child growth standards [51, 52] and for children 10-14 years using the Centers for Diseases Control and Prevention (CDC) growth standards [53]. The CDC growth standards were used for children age 10-14 years because this measure was not available in the WHO growth standards. CD4 counts or CD4 percentage cut were categorized into immune suppression level (no/mild, moderate or severe) for age according to the WHO classification [42, 54]. The year of initiation was categorized as 2014-2015 and 2016-2017.

Data analysis

Baseline characteristics at ART initiations were summarized using frequencies and proportions, and medians and interquartile ranges (IQR), stratified by the timing of ART initiation. We estimated the 24-month cumulative incidence of death and LTFU by time to ART initiation using competing risks survival analysis. Death and LTFU were considered competing risks. Person-time accrued from the ART initiation date to the earliest of LTFU, death, transfer out, 24 months of follow-up or the database closure date (December 31, 2017). We assessed the association between rapid ART initiation and 24-months' mortality and LTFU using sub-distribution hazard regression analysis for competing risks adjusting for confounders. Confounders were selected using stepwise regression using setting the criteria for a variable to enter and stay in the model at p=0.15 and p=0.05, respectively. Known risk factors of loss to follow-up were purposefully

included. Conducted a sensitivity analysis excluding the patients who had only one recorded visit. We also conducted stratified analysis to explore if age modified the association between rapid ART initiation and the outcomes. We imputed missing CD4, WHO clinical stage, WAZ, and hemoglobin values using multiple imputation by chained equations (MICE), using 20 cycles [55, 56].

HUMAN SUBJECTS, ANIMAL SUBJECTS, OR SAFETY CONSIDERATIONS

This study was approved by country-specific institutional review boards, Baylor College of Medicine IRB and University of Texas Health Science Center at Houston Committee for the protection of human subjects.

Confidentiality:

The de-identified data were received from BIPAI and stored in a password-protected computer

JOURNAL ARTICLE 1: Age- and site-specific trends in advanced HIV disease at antiretroviral therapy initiation among children with HIV in eastern and southern Africa: 2003-2017.

Proposed journal for submission: Journal of the International AIDS Society

ABSTRACT

Introduction

The aim of this study was to examine age- and site-specific trends in advanced HIV disease at ART initiation among HIV-infected children. We also examined trends in age and time-to-ART-initiation.

Methods

We analyzed records of HIV-infected children (0-14 years) who initiated ART between 2003-2017 at seven Baylor International Pediatric AIDS Initiative clinics in 6-African countries. Advanced HIV disease was defined as having WHO stage III or IV disease and/or severe immune suppression for age according to WHO criteria. Time-to-ART-initiation was measured from date of entry into care. We analyzed trends in categorical and continuous variables over seven calendar periods from 2003 to 2017 using Cochran-Armitage and Cuzick's test for trend respectively.

Results

20,605 children (31.6% aged <2 years, 20.2% 2-4 years, 26.6% 5-9 years and 21.6% 10-14 years) were included. Half were girls, 33% were from Uganda, 19.8% from Malawi, 13.9% from Lesotho, 13.3% from Tanzania, 10.8% from Eswatini and 9.2% from Botswana. Between 2003-2017, the proportion of children initiating ART with advanced disease declined among ages 5-9 years (58.3% to 39.9%; p<0.01) and 10-14 years (61.9% to 38.1%; p<0.01), remained the same for ages <2 years (72.7% to 70.6%; p=0.1), and increased for ages 2-4 years (59.4% to 62.3%; p<0.01). By site, the proportion decreased in Eswatini (69% to 33%), Lesotho (80% to 34%), Malawi (94% to 33%), and Tanzania (71% to 69%) (all p<0.01), remained the same in Botswana (70% to 52%, p=0.06) and increased in Uganda (46% to 65%; p<0.01).

The median age(IQR) in years at ART initiation increased in Botswana [5.1 (2.2-8.1) to 9.6 (1.5-12.6)], Eswatini [4.3 (1.6-8.1) to 8.5 (1.7-11.7]; Lesotho [3.9 (1.4-7.9) to 8.4 (2.8-11.5)] and Malawi [5.4 (2.2 to 8.5) to 6.6 (1.9-10.8)] (all p's<0.01), remained the same in Tanzania [4.2 (1.5-9.5) to 3.3 (1.4-8.9) ; p=0.1] and declined in Uganda [6.7 (3.8-10.6) to 2.1 (0.8-6.2); p<0.01]. Time-to-ART-initiation reduced among all children [median (IQR):63 (28 to 184) to 5 (0 to 22) days].

Conclusion

Between 2003-2017, disease severity at ART initiation declined among children aged 5-14 years, remained the same in children <2 years, and increased in those aged 2-4 years. Over time, children initiating ART in southern Africa sites were older and less severely ill; those in Eastern Africa sites were younger and more severely ill. In 2016-2017, children initiated ART within the first week in care, but a substantial proportion did so with advanced disease. More efforts are required to diagnose and initiate children on ART early.

INTRODUCTION

In 2017, an estimated 1.8 million children aged<15 years were living with HIV globally, 66% of them in Eastern and Southern Africa (ESA)[1]. Although ESA bears the highest burden of pediatric HIV, the region has made significant progress initiating children with HIV on antiretroviral therapy (ART). In 2017, 59% of children with HIV in the region were receiving ART compared to 52% globally[1]. ART improves survival in children [2-5]; however, disease severity at therapy start is an important prognostic factor. Compared with children with less advanced disease, those who start ART with advanced disease have a higher risk of death[2, 4, 6-11].

To maximize the benefits of ART in children with HIV, the World Health Organization (WHO) provided five sets of normative guidelines on when to initiate ART in children and adolescents between 2003 and 2017[12-15]. With more evidence of the benefits of early therapy in children and better treatment regimens, each updated version of the guidelines expanded treatment initiation criteria to include children with less advanced disease (table 1). The most recent guideline (2015) recommends immediate ART upon diagnosis in all children under 15 years of age. Altogether, the evolution of these guidelines mean that over time children who start ART should have less advanced disease.

Previous studies examining trends in characteristics of children with HIV initiating ART in sub-Saharan African found that, although age and the proportion with advanced disease were declining, a substantial proportion of children still initiated ART with advanced disease[6, 16-20]. Most of these studies examined trends in characteristics up to 2010. Those that examine trends beyond 2010, a period when WHO guidelines for ART initiation have changed most, are few[17, 21]. Moreover, data on age-specific trends are scarce; yet, until 2015, WHO recommended different treatment initiation guidelines by age group (Table 1). Examining trends beyond 2010

will improve our understanding of the impact of more recent WHO guidelines on early treatment initiation. Furthermore, examining age-specific trends may highlight the differential impact of the WHO guidelines on early treatment initiation by age group and identify opportunities to improve early treatment initiation. The objective of our study was to examine age- and site-specific trends in advanced HIV disease among children with HIV who initiated ART in Eastern and Southern Africa between 2003 to 2017. We also examined trends age at ART initiation and overall time-to-ART-initiation.

Table 1: The changes in the WHO recommended criteria for initiating ART in children

<table>
<tr><th>Guideline</th><th>Age</th><th>2003</th><th>2006</th><th>2010</th><th>2013</th><th>2015</th></tr>
<tr><td rowspan="7">Criteria for initiating ART*</td><td><12 months</td><td rowspan="2">CD4 <20%</td><td>CD4<1500 or <25%</td><td rowspan="2">Treat all irrespective of CD4 or WHO stage</td><td rowspan="6">Treat all irrespective of CD4 or WHO stage</td><td rowspan="6">Treat all irrespective of CD4 or WHO stage</td></tr>
<tr><td>12-18months</td><td rowspan="3">CD4<750 or <20%</td></tr>
<tr><td>18-24 month</td><td>CD4 <350 or <20%</td></tr>
<tr><td>24-35 month</td><td rowspan="2">CD4 <350 or <20%</td><td rowspan="2">CD4<750 or <25%</td></tr>
<tr><td>36-59 month</td><td>CD4 <350 or <15%</td></tr>
<tr><td>5-14 years</td><td>CD4 <200 or <15%</td><td>CD4 <200 or <15%</td><td>CD4 count <350</td><td>CD4<500</td></tr>
</table>

*For all the criteria, children with WHO clinical stage 3 or 4 HIV disease were eligible irrespective of age or CD4 cell criteria

METHODS

Study design, setting, and participants

We conducted a pooled cross sectional study and trend analysis of the proportional of children with advanced HIV disease at ART initiation and time to ART initiation in seven cohorts of children with HIV who initiated ART between 2003-2017. The cohorts were defined by the calendar periods of ART initiation (2003-2005, 2006-2007, 2008-2009, 2010-2011, 2012-

2013, 2014-2015, and 2016-2017 which are a proxy for when WHO guidelines were implemented in the study sites.

The children were from seven Baylor International Paediatric AIDS Initiative (BIPAI) centers of excellence (COE's) in six countries in Eastern and Southern Africa (Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda). BIPAI started each COE in partnership with the host governments. The first clinics were started in 2003 in Botswana and Uganda, and later in 2004 in Malawi, 2006 in Lesotho and Swaziland and 2010 in Tanzania (2 COE'S). These COEs provide free HIV prevention, care, and treatment services in line with country-specific guidelines that are adapted from WHO guidelines, and they use a standardized electronic medical records system.

We included all ART-naïve children with HIV aged <15 years who initiated ART between 1 January 2003 and 31 December 2017 at the COEs. Additionally, children exposed to antiretroviral prophylaxis for preventing mother to child HIV transmission were included. The data were de-identified from routine patient management records, which were extracted and pooled electronically.

Variables and definitions

The baseline variables at ART initiation included age, sex, weight, entry point to care, WHO clinical stage and CD4 count, CD4 percent, and weight-for-age z-scores (WAZ). The entry point to care were the prevention of mother to child HIV transmission(PMTCT) clinic, inpatient ward/TB clinic(IPD/TB), outpatient department(OPD), voluntary counseling and testing(VCT), and referrals from other health facilities and outreaches(Others). WHO clinical stage and CD4 were considered to be "at ART initiation" if they were taken on or at a date closest to the ART initiation date within a window of 6-months before until 1-month after ART initiation. Weight

were those taken ± 1months of ART initiation. WAZ for children aged < 10 years were computed using the WHO child growth standards[22, 23] and for children aged 10-14 years, the Centers for Diseases control and prevention (CDC) growth standards were used[24]. The CDC growth standards were used for children ≥ 10 years because the WAZ scores were not available in the WHO child growth standards.

Advanced HIV disease was defined as having WHO clinical stage III or IV disease and/or severe immune suppression for age (CD4% < 25% for children <1 year of age, <20% for children aged 1-3yrs, < 15% for children 3-5 years and <15% or CD4 count <200 cell/mm^3 for children aged 5-14 years)[25, 26].Time to ART initiation was computed from the date of entry into care to the date of ART initiation. The dates of entry into care were grouped into similar calendar periods as the years of ART initiation.

Data analysis

We summarized characteristics at ART initiations using medians (interquartile ranges [IQR]) and proportions for continuous and categorical variables respectively. The characteristics at ART initiation were analyzed by calendar period of ART initiation. Trends in proportions of children with advanced disease and Trends in time to ART initiation over the ordered calendar periods were assessed using Cochran-Armitage test and Cuzick's test for trend respectively. We examined trends in advanced HIV disease overall, by age-group (<2 years, 2-4 years, 5-9 years and 10-14 yrs.) and country. The data from two sites in Tanzania were combined.

Ethical approval

This study was approved by country-specific institutional review boards, Baylor College of Medicine IRB and University of Texas Health Science Center at Houston Committee for the protection of human subjects.

RESULT

Between 2003 and 2017, 20,605 ART-naïve children initiated ART in seven BIPAI COEs in the six African countries and were included in the analysis. Table 2 shows the characteristics and entry points to care for all children by country. The largest number of children were initiated in Uganda (33%), followed by Malawi (19.8%), Lesotho (13.9%), and Tanzania's 2 COE's (13.3%), Eswatini (10.8%) and Botswana (9.2%). The median (IQR) age at ART initiation was 4.7 (1.6 to 9.3) years, range across COEs 3.6 to 5.7 years. The proportion of boys and girls was similar overall and across COEs. The number of children initiating ART increased from 1,920 in 2003-2005, peaked at 3,861 in 2010-11 and declined after that to 2,018 in 2016-17 (Supplementary Table 1). The changes in the number of children initiating ART were similar in all countries. The median (IQR) time from enrollment to ART initiation decreased from a peak of 63 (28 to 184) days in 2008-2009 to 5 (0 to 22) days in 2016-2017, $p<0.01$ (Supplementary Table 1).

Table 2: Characteristics at antiretroviral therapy initiation of children with HIV from 6 countries in Eastern and Southern Africa by calendar period of ART initiation: 2003-2017

Period	Overall N=20,605	Botswana N=1893	Eswatini N=2222	Lesotho N=2870	Malawi N=4076	Tanzania N=2738	Uganda N=6806
Age, median (IQR) years	4.7 (1.5 to 9.3)	5.7 (1.6 to 10)	4.9 (1.5 to 9.4)	5.1 (1.4 to 9.7)	3.6 (1.5 to 8.6)	3.9 (1.4 to 9.1)	5 (1.8 to 9.3)
Age group n(%)							
< 2 year	6513(31.6)	552(29.2)	707(31.8)	954(33.2)	1425(34)	1004(36.7)	1871(27.5)
2-4 years	4170(20.2)	312(16.5)	420(18.9)	471(16.4)	919(23)	495(18.1)	1553(22.8)
5-9 years	5476(26.6)	548(28.9)	614(27.6)	777(27.1)	969(23.8)	674(24.6)	1895(27.8)
10-14 years	4446(21.6)	481(25.4)	483(21.7)	668(23.3)	763(18.7)	565(20.6)	1487(21.9)
Sex							
Female (%)	10343(50.2)	949(50.2)	1069(48.1)	1438(50.1)	1975(48.5)	1409(51.5)	3503(51.5)
Advanced disease, n	20042	1849	2201	2854	3975	2697	6466
Yes (%)	12411(61.9)	1265(68.4)	1445(65.7)	1683(59.0)	2747(69.1)	2033(75.4)	3238(50.1)
WHO stage III/IV ,n	18884	1729	2154	2851	3949	2695	5506
Yes (%)	11449(60.6)	1231(71.2)	1314(61)	1440(50.5)	2522(63.9)	1928(71.5)	3017(54.8)
Severe immune suppression ,n	17703	1554	2130	2655	2996	2441	5927
Yes (%)	3593(20.3)	179(11.5)	481(22.6)	606(22.8)	830(27.7)	513(21.0)	984(16.6)
WAZ, n	20279	1849	2190	2854	4037	2737	6615
median	-2.0	-2.0	-1.7	-2.3	-2.2	-2.4	-1.8
IQR	-3.2 to -1.1	-3.0 to -1.1	-2.8 to -0.8	-3.4 to -1.4	-3.4 to -1.2	-3.6 to -1.3	-2.9 to -0.8
WAZ<-3sd, yes (%)	5871(29.0)	464(25.1)	483(22.1)	946(33.2)	1380(34.2)	988(36.1)	1610(24.3)
Care entry point§, n	20049	1840	2196	2518	4049	2701	6745
PMTCT	726(3.6)	169(9.2)	12(0.5)	95(3.8)	256(6.3)	130(4.8)	64(1.0)
PITC	7544(37.6)	922(50.1)	83(3.8)	217(8.6)	2928(72.3)	572(21.2)	2822(41.8)
VCT	6904(34.5)	627(34.1)	1982(90.3)	2145(85.2)	404(10.0)	1267(46.9)	479(7.1)
Other	4875(24.3)	122(6.6)	119(5.4)	61(2.4)	461(11.4)	732(27.1)	3380(50.1)

§ PMTCT- prevention of mother to child HIV transmission clinic;IPD-inpatient department;OPD-outpatient department;TB-Tuberculosis unit; VCT-voluntary counseling and testing; others - referrals from other health facilities and outreach.

Trends in age at ART initiation

Overall, age at ART initiation fluctuated over time and the change was not significant; however, it decreased in some countries, remained stable in some, and increased in others. The median (IQR) age changed from 5.9 (2.9-9.2) years in 2003-05 to 4.2 (1.3-9.9) years in 2016-2017 but the change was not significant; p=0.9 (Figure 1a, supplementary table 1). The median age initially decreased between 2003 and 2009, then increased until 2014-15 and declined again in 2016-17 (Figure 1a). In Uganda, the median age (IQR) declined from 6.7 (3.8-10.6) years in 2003-2005 to 2.1 (0.8-6.2) years in 2016-17; p<0.01 with fluctuations similar to those observed in the overall median age, while in Tanzania the median age was the same [4.2 (1.5-9.5) years in 2010-2011 to 3.3 (1.4-8.9) years; p=0.1] (Figure 1a, supplementary table 1). In the other countries the median age increased: Botswana [5.1 (2.2-8.1) years to 9.6 (1.5-12.6) years; p<0.01]; Eswatini [4.3 (1.6-8.1) years to 8.5 (1.7-11.7) years; p<0.01]; Lesotho [3.9 (1.4-7.9) years to 8.4 (2.8-11.5) years; p<0.01] and Malawi (5.4 (2.2 to 8.5) years to 6.6 (1.9-10.8) years; p<0.01) (Figure 1b, supplementary table 1).

Overall, the proportions of children aged <2 years and those aged 10-14 years at ART initiation increased over time (supplementary table 1); however, similar to the median age, there were variations across countries. Only Botswana had an increase in both proportions (supplementary table 1). In Malawi, the proportion of infants decreased, but the proportion of adolescents increased, while in Uganda the reverse was true (supplementary table 1). Eswatini and Lesotho had no significant change in the proportion of infants but an increase in the proportion of adolescents while Tanzania had no significant change in both proportions (supplementary table 1).

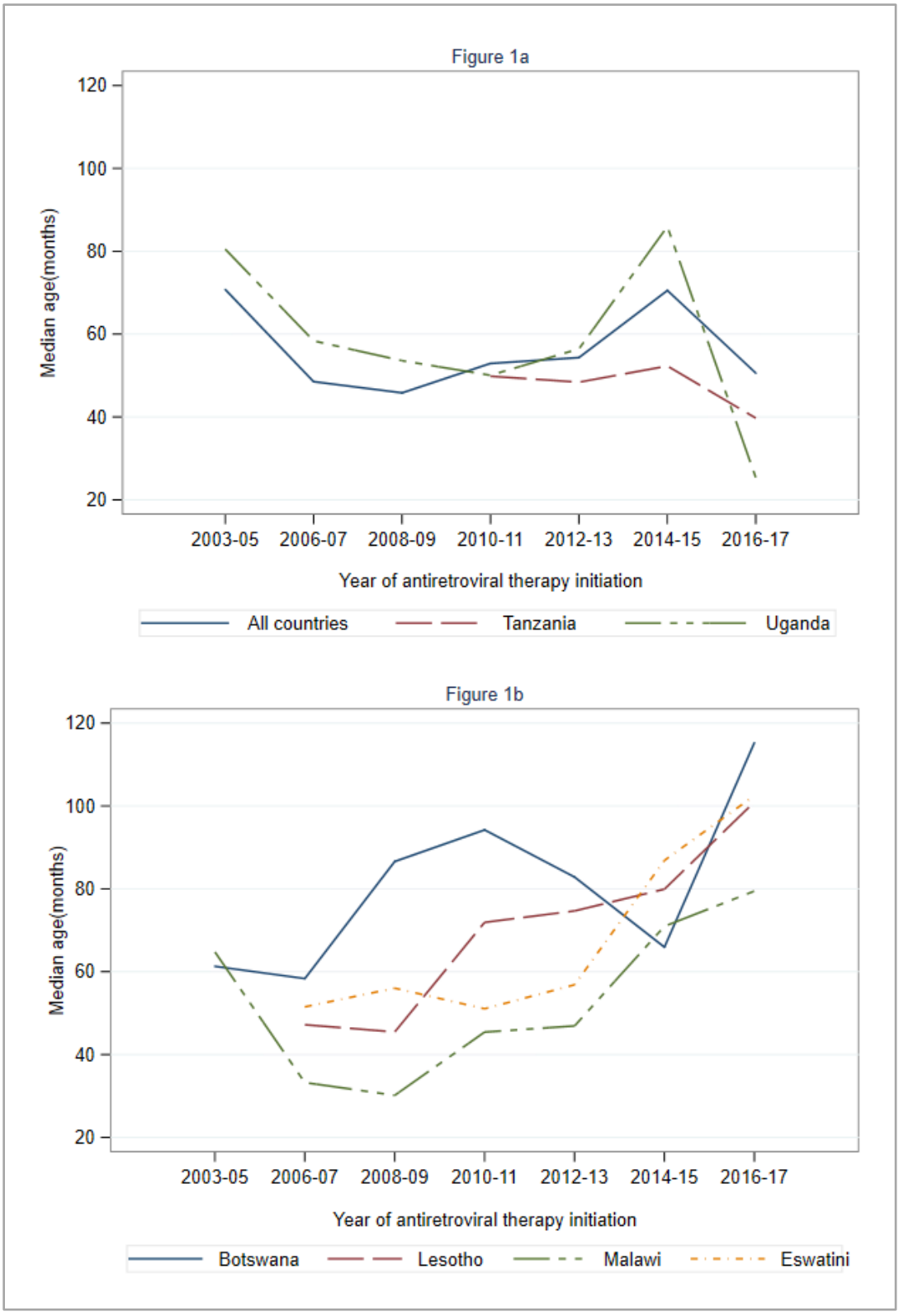


Figure 1: The median ages at initiation by calendar period. (a) in all countries, Tanzania and Uganda; (b) in Botswana, Lesotho, Malawi, and Eswatini

Age-specific trends in advanced disease at ART initiation

Overall, there was a decline in the proportion of children with advanced disease but the trend varied by age group. The proportion of children with advanced disease declined from 65.3% in 2003-05 to 59.5% in 2016-17; p<0.01 (Fig 2a, supplementary table 2). Initially, the proportion plateaued between 2003 and 2013, and it declined after that.

By age group, the proportion remained the same in children <2years (72.7% to 70.6%; p=0.1), increased slightly in children aged 2-4 years (59.4% to 62.3%; p<0.01), but decreased in children aged 5-9 years (58.3% to 39.9%; p<0.01) and among adolescents aged 10-14 years (61.9% to 38.1%; p<0.01) (Fig 2b, supplementary table 2). Although the trend was insignificant among infant, the proportions fluctuated over time. The proportion initially declined from 2003-2011, then it increased to a peak in 2014-2015, and then declined. The proportion in those 2-4 years increased to a peak in 2012-13 and then declined. The proportion in those aged 5-9 and 10-14 plateaued from 2003 to 2013 and declined after that.

Site-specific trends in advanced disease at ART initiation

By country, the proportion of children who initiated ART with advanced disease decreased in all the countries except Botswana where it remained the same and in Uganda where it increased. Among countries where the proportion decreased, the magnitude of the decline varied. The proportion decreased by nearly two-thirds in Malawi (94% to 33%; p<0.01), by half in Eswatini (69% to 33%; p<0.01) and Lesotho (80% to 34%; p<0.01) (Fig 2c, supplementary table 1), and by 12% in Tanzania (79% to 69%; p <0.01) (Fig 2d, supplementary table 1). In Botswana, the proportion remained similar (70% to 52%, p<0.06) while in Uganda, the proportion increased by 40% (46% to 65%; p<0.01). (Figures 2c-2d, supplementary table 1). At the end of the analysis period, more than half of the children in Tanzania, Uganda, and Botswana initiated ART with advanced disease.

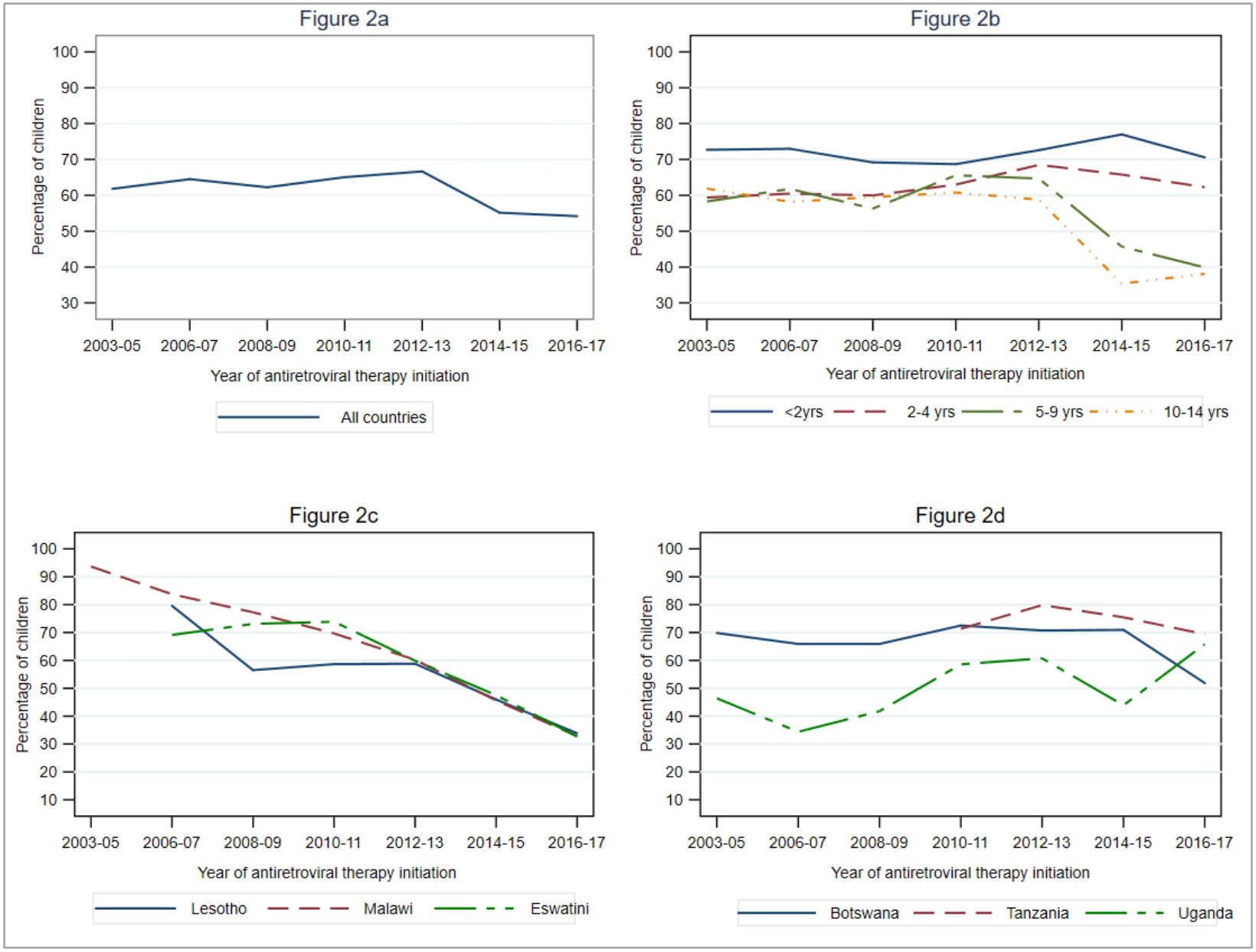


Figure 2: The proportion of children with advanced HIV disease at ART initiation by calendar period. (a) All the six countries combined (b) By age group (c and d) by country.

DISCUSSION

This study of 20,605 children with HIV from seven BIPAI COE's in six countries in ESA documents trends in age and advanced HIV disease at ART start between 2003 and 2017. We found that disease severity at ART initiation among children aged 5-14 years has declined, remained the same in children <2 years and has increased in those aged 2-4 years. Over time, children initiating ART in most Southern Africa sites are older, and less severely ill, while those in Eastern Africa sites are younger and more severely ill. In 2016-2017, children initiated ART within the first week in care but a substantial proportion especially those aged <5yrs still initiated ART with advanced disease. More efforts are required to diagnose and initiate children on ART early.

Although the change in age over time was not significant, the fluctuations over time may reflect changes in WHO guidelines and MTCT rates. The initial decline in median age between 2006 and 2009 is likely due to increased access to early infant diagnosis and WHO recommendation to initiate ART immediately in all children <2 years[13]. As a result, more young children were identified and initiated on ART as is evidenced by the doubling of the proportion of children <2 years between 2006 and 2009 (Table 3). This initial decline is similar to that reported in previous studies[6, 17, 19, 21]. After 2009, we observed an increase up to a peak in 2014-15. During that period, we observe a decline in the proportion of infants and an increase in the proportion of adolescents hence increased median age. There are two possible explanations for this increase. First, from 2010 onwards, new pediatric infections began to decrease in most countries following the implementation of Option A and Option B+ guidelines for PMTCT[1]. Second, the backlog of older children not yet initiated on ART became eligible when the WHO

guidelines were revised to treat all children aged <5 years and all <15yrs in 2013 and 2015 respectively; thus, the median age increased.

The lack of significance in the overall trend in age is also attributable to variations across countries. The median age declined in Uganda, remained the same in Tanzania and increased in the southern Africa sites. The age group of children being initiated likely drives the differences between the countries. In Uganda, the proportion of children <2 years increased over time while, the proportion of adolescents decreased. The reverse was true in Eswatini, Lesotho, and Malawi, whereas in Botswana both proportions increased. The spike in median age observed in Uganda in 2014-2015 coincides with the implementation of the test and start guidelines for all children <15 years[27]. Uganda started implementing these guidelines in 2014 while the other countries started in 2016. The increase in age at ART initiation in southern Africa is a concern. Although it is possible that due to a significant reduction in MTCT rate in these countries, the older children being diagnosed now are the long-term progressors who missed PMTCT when they were born. However, there might be a possibility of sexual transmission, especially in young adolescents. Over 50% of the data on mode of transmission were missing and we cannot ascertain the possibility of sexual transmission.

Overall, the proportion of children with advanced disease at ART initiation declined over time. This finding is similar to those previously reported[6, 16-18]. However, our study found that the decline observed by examining the proportion in all children (0-14yrs) together masks age disparities in trends. We found that the proportion with advanced disease at ART initiation remained the same in children <2 years, increased in children aged 2-4 years and declined in children aged 5-14 years (Fig 2b). The plausible explanation for the constant proportion of children <2 years with advanced disease is disease progression in these children is rapid, and by

the time of diagnosis, most may have progressed to advanced disease. A study on disease progression in children with HIV showed that by one year of age, 80% of these children have shown signs of HIV and 55% have progressed to advanced disease[28]. Additionally, a closer examination of the trend in children <2 years shows a decline in the proportion of those with advance disease between 2006 and 2011 (Fig 2b). This decline is likely related to the increased availability of EID and the WHO recommendation to treat all children under 2-years irrespective of disease severity[13]. Similar declines have been reported among infants in southern Africa[9, 18]. The increase in the proportion of children <2 years with advanced disease at ART initiation after 2011 occurred likely because over time, more children <2 years were being diagnosed in the inpatient wards than through PMTCT (table 3). Children identified in inpatient wards are more likely to have advanced disease than those identified through PMTCT.

Among children aged 2-4 years, the proportion of those with advanced disease increased slightly. As seen among the children <2 years, this increase is likely because increasingly more children 2-4 years are being identified through PITC than PMTCT (table 3). Among the children 5-14 years, we observed decline, which happened after 2013 and is likely due to the implementation of the 2013 and 2015 WHO guidelines. The 2013 WHO guidelines expanded the CD4 threshold for initiating ART in these children to <500 cells/mm^3 and in 2015 recommended immediate ART upon diagnosis in these children[14, 15]. Thus, more children who did not have advanced disease became eligible for ART and were initiated, leading to a decline in the proportion of children with advanced disease at treatment initiation.

Similar to age-specific trends, we observed differences in country-specific trends of the proportion of children with advanced disease. There was a decline in the proportion of children initiating ART with advanced disease in Eswatini, Malawi, Lesotho, and Tanzania, while the

proportion remained the same in Botswana and increased in Uganda. The differences may be attributed to the changes in the age of children initiating ART and entry point to care. As we observed earlier, the proportion of younger children who initiated ART with advanced disease was higher than that in older children (Fig 2b), and studies show that patients identified through provider-initiated testing and counseling (PITC) in inpatient wards and outpatients have higher odds of having advanced disease than those identified through voluntary counseling and testing VCT)[29]. The countries where the proportion of children with advanced disease declined were those where the median age increased and/or enrolled more children through VCT, while in Uganda where the proportion increased, the median age declined and a significant proportion of children in later years entered care through PITC (Table 3). The scenarios in Botswana and Tanzania are different from those in other countries. For example, in Botswana, although the median age increased over time, the proportion of those with advanced disease remained high and did not change mainly because most of the children were identified through PITC. In Tanzania on the other hand, there was a decline in the proportion of children initiating ART with advanced disease although the median age remained the same. Importantly, the decline in Tanzania was slight and in 2016/2017, it had the highest number of children initiating treatment with advanced disease (69.4%).

Despite some of the declines observed, the proportion of children initiating ART with advanced disease is still a concern. The proportion of children with advanced disease in 2016-2017 is much higher than observed in central Africa [17] and Europe[30]. Moreover, we found that in 2016/2017 children initiated ART within five days of entry into care (Fig 1a), meaning most children who initiated ART with advanced disease had advanced disease at entry into care. Our findings highlight the need to intensify efforts to diagnose and initiate ART early before children

develop advanced disease. The benefits of initiating ART with less advanced disease compared to advanced disease include better survival [2, 6, 8, 30-33] and better growth and development [34-36]. In order to improve early diagnosis of HIV in children, programs should focus not only on testing children whose mothers are in the PMTCT program but should increase efforts to find those whose mothers missed PMTCT. The infants whose mothers missed PMTCT can be identified by providing infant testing in immunization clinics[37] and implementing provider-initiated testing in pediatric inpatient wards and outpatient clinics[38-40]. Using the point of care early infant diagnosis testing could improve linkage to treatment and reduce pre-treatment loss to follow-up[41, 42].

Our study has multiple strengths: First, it included data for 15 years, which spans over 5-periods of WHO guidelines implementation including the most recent "test and start" guidelines. This has enabled us to how characteristics of children have changed because of WHO guideline changes. Second, by examining age-specific trends in advanced disease, we are able to show how guideline changes differentially affected the age groups. Lastly, our study had a large sample (20,605) of children from six countries in ESA, which enabled us to compare trends across countries. Nevertheless, our study has several limitations, which should be considered when interpreting our results. First, there was substantial missing data (30%) for CD4 count and CD4 percent especially during the implementation of the test and start guidelines for all children (2015-2017). However, during that period, less than 5% of patients had missing data on the WHO clinical stage, and hence most patients could be classified as having advanced disease or not using clinical stage. Second, there is potential for selection bias since these COE's received children from referral hospitals, and the patients at referral hospitals are usually very sick compared to primary care centers. The proportion of children with advanced disease in our study may not be representative of general trends for that country due to this referral pattern. Third, the

generalizability of our findings to the countries where these clinics are located may be limited because the COEs are well resourced and better staffed compared to primary healthcare facilities in those countries. Notwithstanding, in some countries, these COEs serve a significant proportion of children with HIV in the country which enhances representativeness, e.g., about 30% of all children with HIV in Botswana receive care in the COE and about 22% in Lesotho. Lastly, although changes in WHO guidelines explain some of the changes we observe, our study is purely descriptive, and it is difficult to attribute causation to guideline changes. Other interrelated factors like increased health worker training and increased programmatic funding may have contributed to the changes.

CONCLUSION

Our study shows that between 2003 and 2017, disease severity at ART initiation among children aged 5-14 years has declined, remained the same in children <2 years and has increased in those aged 2-4 years. Over time, children initiating ART in most Southern Africa sites are older, and less severely ill, while those in Eastern Africa sites are younger and more severely ill. In 2016-2017, children initiated ART within the first week in care but a substantial proportion especially those aged <5yrs still initiated ART with advanced disease. More efforts are required to diagnose and initiate children on ART early.

Supplementary table 1: Characteristics at antiretroviral therapy initiation and entry point to care of children with HIV overall and by country between 2003-2017 §

Characteristic	Period of ART initiation							p for trend ¥
	2003-05	2006-07	2008-09	2010-11	2012-13	2014-15	2016-17	
All Countries								
N	1920	3113	3363	3861	3223	3107	2018	
Time to ART, median (IQR) days	45 (15 to 142)	55 (28 to 126)	63 (28 to 184)	48 (18 to 259)	21 (7 to 114)	16 (3 to 356)	5 (0 to 22)	<0.01
Age, Median(IQR) years	5.9 (2.8 to 9.2)	4 (1.6 to 8.4)	3.8 (1.4 to 8.5)	4.4 (1.5 to 9.2)	4.5 (1.4 to 9.7)	5.9 (1.7 to 10.3)	4.2 (1.3 to 9.9)	0.9
<2yrs	332(17.3)	999(32.1)	1181(35.1)	1276(33)	1077(33.4)	905(29.1)	743(36.8)	<0.01
2-4 yrs	480(25)	732(23.5)	712(21.2)	799(20.7)	602(18.7)	517(16.7)	328(16.3)	
5-9 yrs	712(37.1)	857(27.5)	838(24.9)	983(25.5)	789(24.5)	851(27.4)	446(22.1)	
10-14yrs	396(20.6)	525(16.9)	632(18.8)	803(20.8)	755(23.4)	834(26.8)	501(24.8)	<0.01
Advanced disease, n	1832	3025	3282	3750	3174	3051	1928	
Yes (%)	1132(61.8)	1952(64.5)	2043(62.3)	2440(65.1)	2116(66. 7)	1683(55.2)	1045(54.2)	<0.01
Entry point, n	1866	2821	3308	3780	3198	3074	2002	
PMTCT	66(3.5)	127(4.5)	93(2.8)	130(3.4)	119(3.7)	117(3.8)	74(3.7)	
PITC	585(31.4)	810(28.7)	1242(37.6)	1510(39.9)	1317(41.2)	1260(41)	820(40.9)	
Self-referral/VCT	487(26.1)	1090(38.6)	1361(41.1)	1155(30.6)	1105(34.6)	1020(33.2)	686(34.3)	
Other	728(39)	794(28.2)	612(18.5)	985(26.1)	657(20.5)	677(22)	422(21.1)	
Botswana								
N	**779**	**186**	**271**	**263**	**164**	**124**	**106**	
Time to ART, median (IQR) days	17 (7 to35)	14 (0 to 41)	16 (0 to 151)	14 (1 to 58)	16 (6 to 45)	14 (5 to 54)	9 (3 to 53)	0.6
Age, Median(IQR) years	5.1 (2.2 to 8.1)	4.9 (0.8 to 9.9)	7.2 (1.5 to 10.9)	7.9 (1.0 to 11.2)	6.9 (0.8 to 12.1)	5.5 (0.8 to 11.8)	9.6 (1.5 to 12.6)	<0.01
<2yrs	171(22)	73(39.3)	78(28.8)	87(33.1)	66(40.2)	46(37.1)	31(29.3)	<0.01
2-4 yrs	211(27.1)	22(11.8)	27(10)	20(7.6)	7(4.3)	14(11.3)	11(10.4)	
5-9 yrs	307(39.4)	46(24.7)	74(27.3)	62(23.6)	29(17.7)	17(13.7)	13(12.3)	
10-14yrs	90(11.6)	45(24.2)	92(34)	94(35.7)	62(37.8)	47(37.9)	51(48.1)	<0.01
Advanced disease, n	756	173	264	262	164	124	106	
Yes (%)	528(69.8)	114(65.9)	174(65.9)	190(72.5)	116(70.7)	88(71)	55(51.9)	0.06
Entry point , n	754	182	265	256	159	119	105	
PMTCT	46(6.1)	21(11.5)	35(13.2)	35(13.7)	16(10.1)	8(6.7)	8(7.6)	
PITC	266(35.3)	62(34.1)	128(48.3)	167(65.2)	123(77.4)	93(78.2)	83(79)	
Self-referral/VCT	406(53.9)	87(47.8)	83(31.3)	24(9.4)	11(6.9)	11(9.2)	5(4.8)	
Other	36(4.7)	12(6.6)	19(7.2)	30(11.7)	9(5.6)	7(5.9)	9(8.6)	

§ n is the available data for each variable. ¥ The p-values are from Cochrane Armitage test and Cuzick's test for trends of proportions and medians respectively over ordered calendar periods of ART initiation.

Supplementary table 1: continued

Characteristic	Period of ART initiation							p for trend ¥
	2003-05	2006-07	2008-09	2010-11	2012-13	2014-15	2016-17	
Malawi								
N	**221**	**779**	**892**	**903**	**569**	**405**	**307**	
Time to ART, median (IQR) days	30 (13 to 75)	43 (25 to 90)	71 (36 to 166)	66 (21 to 332)	22 (4 to 155)	17 (2 to 362)	7 (0 to 175)	<0.01
Age, Median(IQR) years	5.4 (2.2 to 8.5)	2.77 (1.4 to 7.4)	2.51 (1.2 to 6.6)	3.79 (1.6 to 8.5)	3.91 (1.4 to 9.4)	5.91 (2.0 to 10.7)	6.62 (1.9 to 10.8)	<0.01
<2yrs	49(22.2)	303(38.9)	375(42)	307(34)	201(35.3)	106(26.2)	84(27.4)	0.15
2-4 yrs	52(23.5)	188(24.1)	219(24.6)	215(23.8)	110(19.3)	84(20.7)	51(16.6)	
5-9 yrs	75(33.9)	170(21.8)	181(20.3)	226(25)	134(23.6)	101(24.9)	82(26.7)	
10-14yrs	45(20.4)	118(15.2)	117(13.1)	155(17.2)	124(21.8)	114(28.2)	90(29.3)	<0.01
Advanced disease, n	221	775	875	884	543	388	289	
Yes (%)	207(93. 7)	649(83.7)	676(77.3)	616(69.7)	327(60.2)	177(45.6)	95(32.9)	<0.01
Entry point, n	221	768	890	894	568	402	306	
PMTCT	20(9.1)	93(12.1)	48(5.4)	52(5.8)	21(3.7)	11(2.7)	11(3.6)	
PITC	80(36.2)	417(54.3)	727(81.7)	686(76.7)	454(79.9)	312(77.6)	252(82.3)	
Self-referral/VCT	73(33)	183(23.8)	37(4.1)	43(4.8)	27(4.8)	30(7.5)	11(3.6)	
Other	48(21.7)	75(9.8)	78(8.8)	113(12.7)	66(11.6)	49(12.2)	32(10.5)	
Uganda								
N	**920**	**960**	**863**	**1415**	**920**	**1085**	**643**	
Time to ART, median (IQR) days	121 (56 to282)	93 (42 to 280)	92 (43 to 417)	51 (24 to 489)	15 (6 to 266)	14 (2 to 1204)	2 (0 to 7)	<0.01
Age, Median(IQR) years	6.7 (3.8 to 10.6)	4.9 (2.0 to 9.1)	4.5 (1.7 to 8.8)	4.2 (1.6 to 8.5)	4.7 (1.7 to 9.3)	7.2 (2.2 to 10.4)	2.1 (0.8 to 6.2)	<0.01
<2yrs	112(12.2)	235(24.5)	254(29.4)	446(31.5)	259(28.1)	254(23.4)	311(48.4)	<0.01
2-4 yrs	217(23.6)	248(25.8)	216(25)	353(25)	215(23.4)	182(16.8)	122(19)	
5-9 yrs	330(35.8)	279(29.1)	226(26.2)	354(25)	238(25.9)	341(31.4)	127(19.7)	
10-14yrs	261(28.4)	198(20.6)	167(19.4)	262(18.5)	208(22.6)	308(28.4)	83(12.9)	<0.01
Advanced disease, n	855	898	811	1335	912	1061	594	
Yes (%)	397(46.4)	309(34.4)	339(41.8)	782(58.6)	554(60.8)	466(43.9)	391(65.8)	<0.01
Entry point, n	891	949	856	1406	918	1082	643	
PMTCT	0(0)	6(0.6)	0(0)	18(1.3)	17(1.9)	17(1.6)	6(0.9)	
PITC	239(26.8)	272(28.7)	362(42.3)	558(39.7)	503(54.8)	582(53.8)	306(47.6)	
Self-referral/VCT	8(0.9)	5(0.5)	7(0.8)	129(9.2)	95(10.3)	115(10.6)	120(18.7)	
Other	644(72.3)	666(70.2)	487(56.9)	701(49.8)	303(33)	368(34)	211(32.8)	

§ n is the available sample size for each variable. ¥ The p-values are from Cochrane Armitage test for categorical variables and Cuzick's test for continuous variables over ordered calendar periods of ART initiation.

Supplementary table 1: continued

Characteristic	Period of ART initiation						p for trend ¥
	2006-07	2008-09	2010-11	2012-13	2014-15	2016-17	
Eswatini							
N	**565**	**612**	**468**	**206**	**205**	**166**	
Time to ART, median (IQR) days	56 (32 to 113)	56 (28 to 143)	46 (19 to 229)	55 (21 to 269)	42 (16 to 572)	28 (9 to 1367)	0.2
Age, Median (IQR) years	4.29 (1.6 to 8.1)	4.67 (1.5 to 8.8)	4.25 (1.3 to 8.9)	4.74 (1.5 to 10.5)	7.24 (2.0 to 10.8)	8.54 (1.7 to 11.7)	<0.01
<2yrs	172(30.4)	201(32.8)	170(36.3)	69(33.5)	51(24.9)	44(26.5)	0.5
2-4 yrs	136(24.1)	115(18.8)	80(17.1)	39(18.9)	34(16.6)	16(9.6)	
5-9 yrs	177(31.3)	173(28.3)	126(26.9)	39(18.9)	58(28.3)	40(24.1)	
10-14yrs	80(14.2)	123(20.1)	92(19.7)	59(28.6)	62(30.2)	66(39.8)	<0.01
Advanced disease, n	557	610	463	202	204	165	
Yes (%)	385(69.12)	446(73.11)	342(73.87)	121(59.9)	97(47.55)	54(32.73)	<0.01
Entry point, n	550	609	464	204	203	166	
PMTCT	6(1.1)	3(0.5)	3(0.6)	0(0)	0(0)	0(0)	
PITC	37(6.7)	5(0.8)	4(0.9)	1(0.5)	9(4.4)	27(16.3)	
Self-referral/VCT	480(87.3)	579(95.1)	430(92.7)	193(94.6)	180(88.7)	120(72.3)	
Referrals from other health facilities/outreach	27(4.9)	22(3.6)	27(5.8)	10(4.9)	14(6.9)	19(11.4)	
Lesotho							
N	**623**	**725**	**519**	**396**	**361**	**246**	
Time to ART, median (IQR) days	36 (22 to 79)	42 (21 to 126)	56 (23 to 333)	43 (20 to 189)	29 (14 to 272)	24 (2 to 764)	0.08
Age, Median(IQR) years	3.9 (1.4 to 7.9)	3.8 (1.0 to 8.2)	6.0 (1.3 to 10.2)	6.2 (1.6 to 10.1)	6.7 (1.5 to 10.9)	8.4 (2.8 to 11.5)	<0.01
<2yrs	216(34.7)	273(37.7)	171(33)	134(33.8)	114(31.6)	46(18.7)	0.004
2-4 yrs	138(22.2)	135(18.6)	67(12.9)	46(11.6)	50(13.9)	35(14.2)	
5-9 yrs	185(29.7)	184(25.4)	147(28.3)	112(28.3)	82(22.7)	67(27.2)	
10-14yrs	84(13.5)	133(18.3)	134(25.8)	104(26.3)	115(31.9)	98(39.8)	<0.01
Advanced disease, n	622	722	513	391	361	245	
Yes (%)	495(79.6)	408(56.5)	301(58.7)	230(58.8)	166(46.0)	83(33.9)	<0.01
Entry point, n	372	688	477	389	349	243	
PMTCT	1(0.3)	7(1)	2(0.4)	26(6.7)	42(12)	17(7)	
PITC	22(5.9)	20(2.9)	33(6.9)	36(9.3)	55(15.8)	51(21)	
Self-referral/VCT	335(90.1)	655(95.2)	441(92.5)	326(83.8)	240(68.8)	148(60.9)	
Other	14(3.7)	6(0.9)	1(0.2)	1(0.3)	12(3.4)	27(11.1)	

§ n is the available data for each variable. ¥ The p-values are from Cochrane Armitage test and Cuzick's test for trends of proportions and medians respectively over ordered calendar periods of ART initiation.

Supplementary table 1: continued

[§] n is the available data for each variable. [¥] The p-values are from Cochrane Armitage test and Cuzick's test for trends of proportions and medians respectively over ordered calendar periods of ART initiation.

Characteristic	Period of ART initiation						p for trend[¥]
	2006-07	2008-09	2010-11	2012-13	2014-15	2016-17	
			Tanzania				
N			**293**	**968**	**927**	**550**	
Time to ART, median (IQR) days			20 (10 to 45)	17 (6 to 53)	12 (2 to 41)	3 (0 to 14)	<0.01
Age, Median(IQR) years			4.2 (1.5 to 9.5)	4 (1.4 to 8.9)	4.4 (1.5 to 9.1)	3.3 (1.3 to 8.9)	0.1
<2yrs			95(32.4)	348(36)	334(36)	227(41.3)	0.2
2-4 yrs			64(21.9)	185(19.1)	153(16.5)	93(16.9)	
5-9 yrs			68(23.2)	237(24.5)	252(27.2)	117(21.3)	
10-14yrs			66(22.5)	198(20.4)	188(20.3)	113(20.5)	
Advanced disease, n			293	962	913	529	
Yes (%)			209(71.33)	768(79.83)	689(75.47)	367(69.38)	<0.01
Entry point, n			283	960	919	539	
PMTCT			20(7.1)	39(4.1)	39(4.2)	32(6.0)	
PITC			62(21.9)	200(20.8)	209(22.8)	101(18.7)	
Self-referral/VCT			88(31.1)	453(47.2)	444(48.3)	282(52.3)	
Other			113(39.9)	268(27.9)	227(24.7)	124(23.0)	

Supplementary table 2: Age-specific trends in advanced HIV disease at antiretroviral therapy initiation among children with HIV in all countries: 2003-2017 §

Characteristic	Calendar period of ART initiation							p for trend[¥]
	2003-05 N=1920	2006-07 N=3113	2008-09 N=3363	2010-11 N=3861	2012-13 N=3223	2014-15 N=3107	2016-17 N=2018	
< 2 year, n	318	983	1163	1243	1052	868	698	
Yes (%)	231(72.7)	718(73)	805(69.2)	854(68.7)	764(72.6)	668(77)	493(70.6)	0.1
2-4 years, n	458	713	692	775	597	511	313	
Yes (%)	272(59.4)	431(60.5)	415(60)	488(63)	409(68.5)	336(65.8)	195(62.3)	<0.01
5-9 years, n	682	819	815	952	780	844	426	
Yes (%)	397(58.2)	506(61.8)	459(56.3)	624(65.6)	505(64.7)	386(45.7)	170(39.9)	<0.01
10-14 years, n	374	510	612	780	745	828	491	
Yes (%)	232(62.0)	297(58.2)	364(59.5)	474(60.8)	438(58.8)	293(35.4)	187(38.1)	<0.01

[§] n is the available data for each variable. [¥] The p-values are from Cochrane Armitage test for trends of proportions over ordered calendar periods of ART initiation.

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JOURNAL ARTICLE 2: Long-term survival of HIV-infected children treated with antiretroviral therapy in Eastern and Southern Africa: 2006-2017

Proposed Journal: Lancet HIV

ABSTRACT

Introduction

Despite providing pediatric antiretroviral therapy (ART) for >10 years, data on long-term survival of HIV-infected children receiving ART in resource-limited settings are scarce. We describe 10-year survival and risk factors for early mortality in HIV-infected children receiving ART.

Methods

We conducted a retrospective cohort study of HIV-infected children (0-14 years) who initiated ART between 2006-2017 at seven centers of excellence in Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda. Time to death was measured from the ART initiation date, and children were right-censored at the earliest of either LTFU, transfer out, 10-years of follow-up or database closure date (Dec 31, 2019). We estimated the 10-year survival probability using Kaplan-Meier methods and assessed risk factors for mortality using Cox proportional hazard regression

Results

Among 18,010 children (median age, 4.5 years; girls, 50%; half were girls), 1528 (8.5%) died, 3333 (18.5%) transferred, 1633 (9.1%) were LTFU, and 11,516 (63.9%) remained in care. Half of the deaths were within 6-months of therapy (mortality rate=9.17, 95% CI: 8.55-9.84 per 100 PY). 10-year survival probability %(95%CI) was 88.9 (88.3-89.5) overall, 83.7 (82.5-84.8) in children aged <2 years, 91.9 (90.7-93.0) in those 2-4 years, 92.6 (91.5-93.6) in 5-9 years and 88.8 (9 87.2-90.2) in 10-14 years. The 10-year survival probability in Botswana was 91.7(89.1-93.7), 89.8(88.1-91.2) in Eswatini, 86.9(85.2-88.4) in Lesotho, 86.5(84.9-88.0) in Malawi and 90.7(89.6-91.6) in Uganda. In Tanzania, the 5-year survival probability was 89.5(88.0-90.9). The risk factors of mortality were: baseline age <2 years (aHR 1.41(95% CI: 1.11-1.79) compared to 10-14 years; WHO stage 4 (aHR 2.95(95% CI 2.33-2.72) and stage 3 (aHR 1.36(95% CI: 1.06-1.73) compared to stage 1 and 2 disease; severe (aHR=6.71, 95% CI 5.29-8.52) and moderate (aHR=2.64, 95% CI 1.90-3.66)

immune suppression compared to no/mild immune suppression; and severe underweight (aHR 1.84 (95% CI 1.48-2.29) compared to normal weight-for-age.

Conclusion

10-year survival in children receiving ART is good. Mortality is highest in the first 6-months of ART and young age (<2 years), advanced HIV disease and severe underweight at ART initiation were associated with a higher risk of early mortality. Our findings re-emphasize the need for early infant diagnosis and treatment and close monitoring during the first 6-months of therapy as measures to reduce mortality of HIV-infected children receiving ART.

INTRODUCTION

For nearly one and a half decades, combination antiretroviral therapy (ART) has been the standard approach for treating pediatric HIV in the Eastern and Southern Africa region (ESA). Since its introduction in the region, ART has improved short-term survival of HIV-infected children [1-4]. Additionally, several programmatic improvements that could further improve the survival of children have been implemented. For example, the 2015 WHO recommendation to initiate ART in all children upon diagnosis irrespective of disease severity have been implemented by countries, and more effective pediatric antiretrovirals (ARV's) have become available over time[5].

Despite the improved survival and programmatic improvements, in resource-limited settings, long-term pediatric ART care presents challenges that could affect the success of ART and long-term survival. For example, lack of appropriate pediatric ARV formulations, ARV stock outs, and health care workers need to adjust treatment doses as the child's weight increases; yet, children may not adhere to clinic appointments [6, 7]. Moreover, children are vulnerable because they depend on caregivers, who may be too sick to administer their medicines and as they grow into adolescents, they may not adhere to treatment [8, 9]. All these challenges could lead to poor long-term adherence to ART, which can result in treatment failure, disease progression, and death.

Even with over 10-years' experience providing pediatric ART, data on long-term survival of children initiating ART are mainly from high and middle-income countries, and those from RLS are scarce; yet, challenges of providing pediatric ART in these settings may differ. Studies from high and middle-income countries report 5-10 year mortality rates of 1.2-1.7 deaths per 100 person-years and a survival probability of >94-99% [10-14]. One study from Mozambique that examined survival in children receiving ART reported 8-years survival probability of 90% [15]. Limited data on long-term survival of children receiving ART in RLS precludes our understanding of the impact of ART

programs on long-term survival in HIV infected children, and yet significant investments have been made to improve survival in children with HIV.

The Baylor International Pediatric AIDS Initiative (BIPAI) includes a network of seven clinical centers of excellence (COE) in six countries in Eastern and Southern Africa that have provided pediatric ART for over ten years [16]. Data from the BIPAI network, therefore, provides an opportunity to examine long-term survival of children receiving ART. Our study examined age-specific survival at ten years of ART and risk factors for early mortality in HIV infected children who initiated ART between 2003-2017 in the BIPAI network clinics.

METHODS

Study design, setting, and population

This study was a retrospective cohort study using patient-level data pooled from seven BIPAI COEs in Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda. These COEs are operated in partnership with the respective governments and receive substantial funding for distribution of ART from the Presidential Emergency Plan for AIDS Relief (PEPFAR). They provide free comprehensive HIV/AIDS prevention and treatment services to children and adolescents with HIV. Children at all the COEs receive clinical care at least 3-monthly. Shorter clinic appointments are given at the start of therapy and when medically required. The data at the sites are managed using a standardized electronic medical record system (EMR).

We included children with HIV aged <15 years who initiated ART between January 2006 and June 2017 and had two or more follow-up visits after ART initiation. Children who were ARV experienced (except for exposure to ARVs for PMTCT) at entry into care were excluded. The cohort start date for Tanzania was 2010, corresponding to the period when the clinic became operational.

The individual patient data were pooled electronically, anonymized and transferred to the research team for cleaning and management. Ethical approvals (with a waiver of informed consent) were obtained from the individual country institutional review boards (IRB), Baylor College of Medicine IRB and University of Texas Health Science Center at Houston Committee for the protection of human subjects.

Study variables and definitions

The independent study variables were age, sex, country, weight, height, WHO clinical stage, CD4 count, CD4 percent, weight for age Z-scores (WAZ), BMI for age Z scores (BAZ), ART regimens, TB diagnosis, hemoglobin levels(Hb) and immune suppression level. The child's weight or height was considered to be at ART start if they were taken ± 1month from the ART start date, while WHO stage and CD4 count or percent at ART start were taken on or at a date closest to the ART initiation date within six months before and one month after ART initiation. We computed the WAZ for children aged < 10 years and BAZ for all children using the WHO child growth standards [17, 18]. WAZ for children aged 10-14 years using the Centers for Diseases Control and Prevention (CDC) growth standards [19] because this measure was not available for the age group in the WHO growth standards. CD4 counts or CD4 percentage were categorized into immune suppression levels (no/mild, moderate or severe) for age according to the WHO classification [20, 21]. The calendar period of ART initiation was categorized into three, 4-year periods: 2006-2009, 2010-2013 and 2014-2017 corresponding to WHO guideline periods; 2014-2017 covered two guideline periods.

The main outcome variable was all-cause mortality and was defined as death from any cause including HIV related and non-HIV related deaths. The date of death was extracted from the EMR. If the date was missing, we used the date the chart was closed. Other events that were censored in the analysis were lost to follow-up (LTFU), transfer out and active in care. The patient was considered LTFU if there was a gap of 90 days between their next clinic appointment and the database closure

date (December 31, 2017). The date of LTFU was the chart closure date, and if the chart was not closed, the patient was censored 90 days after the last scheduled appointment. The patient was considered transferred-out if the transfer was documented and the date of transfer was that recorded in the chart.

Statistical analysis

Patient characteristics at ART initiation were described using summary statistics (medians and proportions) by age groups (<2 years, 2-4 years, 5-9 years and 10-14 years). We computed overall mortality rates per 100 person-years(PY) and rates within the first six months of ART, at 6-24 months and after 24 months. Kaplan-Meier estimates for 10-year survival probability was calculated overall, by age group, country, and calendar period of ART initiation; differences in survival curves were tested using the log-rank test. Time to death was computed from the date of ART initiation, and children were right-censored at the earliest of either LTFU, transfer out, 10-years of follow-up or database closure date. We examined risk factors of mortality in the first 6-months and 6-24 months on ART using univariable and multivariable Cox proportional hazard regression models. We limited the analysis to the first 24 months to enable us to examine the effect of the most recent WHO-treatment guidelines (2014-2017) on survival. We used a stepwise regression method to select the most parsimonious model. The criteria for a variable to enter and to stay in the model were $p \leq 0.15$ and $p \leq 0.05$, respectively. Known predictors of death, including WHO clinical stage, immune suppression level, and age were purposefully included in the analysis. We tested the proportional hazards assumption using the Schoenfield test. To avoid loss of information and biased estimates because of missing data, we imputed missing CD4, WHO stage, WAZ, and Hb values using multiple imputation by chained equations (MICE), using 20 cycles[22, 23]. We conducted sensitivity analyses using complete case analysis and competing risks analyses with LTFU as the competing risk.

RESULTS

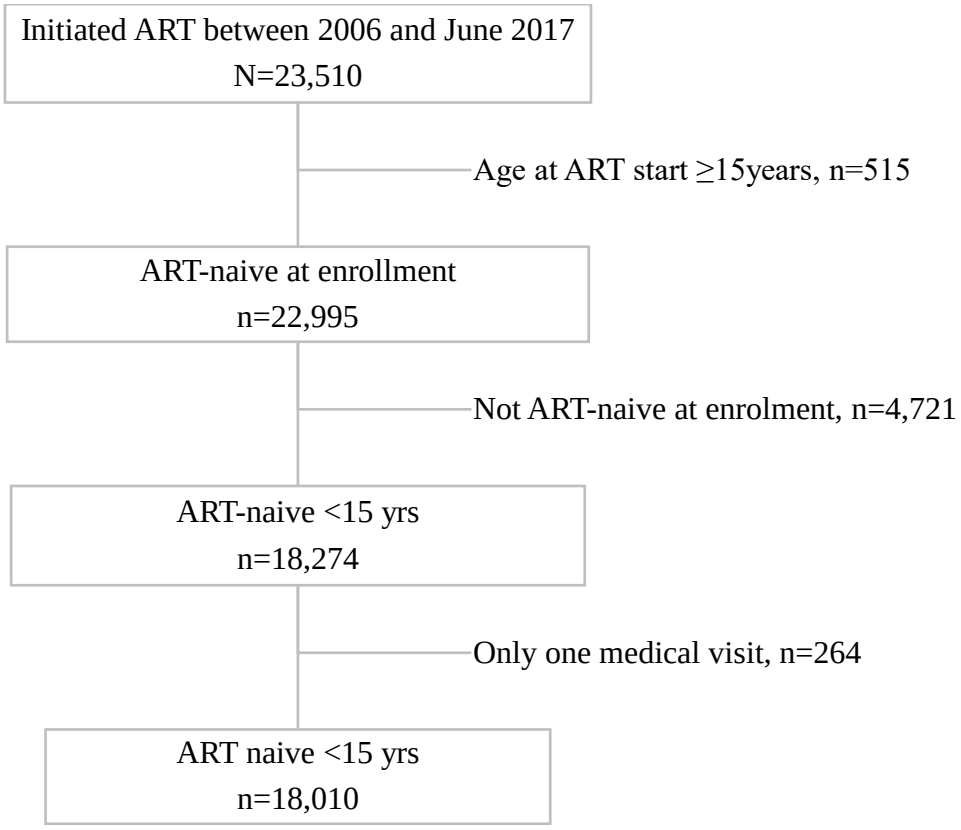
Characteristics of participants

Overall, 23,510 children with HIV initiated ART between January 2006 and June 2017 at the BIPAI COEs, of whom 22,995 were <15 years of age. Of these, 4721 were excluded because they were not ART naïve at the time of enrollment in care at the study sites. These children transferred care to the study sites while they were already receiving ART and we did not have their baseline characteristics at ART initiation. In addition, we excluded 264 children who had only one medical visit after initiating ART, leaving 18,010 who were included in the study (Figure 1).

Table 1 describes patients' characteristics at ART initiation by age group. Of the 18,010 children included in the study, half were girls and the median age was 4.5 [interquartile range (IQR): 1.5-9.4] years. A third of all children were from Uganda and most initiated ART during 2010-2013. Most of the children (32.6%) were aged <2 years, 19.8% were 2-4 years, 25.7% 5-9 years and 21.9% were 10-14 years; 24.2% of all children had stage 4 disease, 17.8% had severe immune suppression, and 28.4% were severely underweight. Stage 4 disease, severe immune suppression and underweight were more frequent in the children <2 years than the other age groups (Table 1). Among all children, 86% initiated ART with nucleoside reverse transcriptase inhibitor (NNRTI) based regimens, but the frequency varied from 70% among infants to 95% among those aged 5-9 years.

The median duration of follow-up was 4.34 (IQR: 1.69-7.47) years with 85,140 person-years (PY) of follow-up overall. Of the overall person-time, 25,076 PY were of children aged <2 years, 18,008 PY aged 2-4 years, 23,522 PY aged 5-9 years and 18,534 aged 10-14 years. During follow-up, 1528 (8.5%) children died, 3333 (18.5%) transferred care to other health facilities, 1633 (9.1%) were LTFU, and 11,516 (63.9%) were still in care by the end of the study. Half of the deaths occurred within six months of ART and 78% within 2-years of ART.

Figure 1: Flow chart



Mortality rates

The mortality rate among all children was 1.79 deaths per 100 PY. Mortality during the first 6 months of receiving ART was 9.17 (95% CI: 8.55-9.84) deaths per 100 PY. The rate declined to 1.95 (95% CI: 1.77-2.14) deaths per 100 PY between 6-month to 2 years and thereafter it reduced to 0.59 (95% CI: 0.53-0.65) deaths per 100 PY. Mortality rates per 100 PY were 17.5 (95% CI: 16-19.2) in children <2 years, 6.8 (95% CI: 5.6-8.1) in 2-4 years, 4.7 (95% CI: 3.9-5.7) in 4-9 years and 4.8 (95% CI: 3.9-5.9) in the 10-14 year old. The combined probability of surviving up to 10-years on ART was 88.9% (95% CI: 88.3%-89.5%). Children <2 years of age had the lowest 10-year survival probability [83.7% (95% CI: 82.5%-84.8%)] as compared to 91.9% (95% CI: 90.7%-93.0%) in those 2-4 years, 92.6 % (95% CI: 91.5%-93.6%) in 5-9 years and 88.8% (95% CI: 87.2%-90.2%) (Figure 2).

Table 1. Patient characteristics at ART start stratified by age.

Characteristic	Total (N=18010)	<2 years (N=5869)	2-4 years (N=3570)	5-9 years (N=4631)	10-14 years (N=3940)
Age, median(IQR) years	4.5(1.5-9.4)	1(0.6-1.5)	3.2(2.5-4.1)	7.6(6.3-8.8)	12.2(11.1-13.4)
Sex, n (%)					
Female	9046(50.2)	2916(49.7)	1711(47.9)	2313(50)	2106(53.5)
Male	8964(49.8)	2953(50.3)	1859(52.1)	2318(50.1)	1834(46.6)
WHO clinical stage, n (%)					
1&2	6783(37.7)	1810(30.8)	1288(36.1)	1792(38.7)	1893(48.1)
3	5607(31.1)	1650(28.1)	1186(33.2)	1673(36.1)	1098(27.9)
4	4363(24.2)	2036(34.7)	812(22.8)	812(17.5)	703(17.8)
missing	1257(7)	373(6.4)	284(8)	354(7.7)	246(6.2)
Hemoglobin(mg/dl)	11.4(10-12.4)	10.6(9.2-11.8)	11.3(9.9-12.3)	11.7(10.7-12.7)	12.2(11.1-13.1)
Immune Suppression, n (%)					
None/mild	10490(58.3)	2791(47.6)	2171(60.8)	3182(68.7)	2346(59.5)
moderate	1891(10.5)	592(10.1)	286(8)	478(10.3)	535(13.6)
Severe	3206(17.8)	1567(26.7)	654(18.3)	429(9.3)	556(14.1)
missing	2423(13.5)	919(15.7)	459(12.9)	542(11.7)	503(12.8)
Underweight, n (%)					
None/mild/mod	12662(70.3)	3287(56)	2741(76.8)	3744(80.9)	2890(73.4)
Severe	5120(28.4)	2546(43.4)	775(21.7)	797(17.2)	1002(25.4)
missing	228(1.3)	36(0.6)	54(1.5)	90(1.9)	48(1.2)
ART regimen, n (%)					
NNRTI based	15481(86)	4123(70.3)	3168(88.7)	4430(95.7)	3760(95.4)
PI- based/other	2529(14)	1746(29.7)	402(11.3)	201(4.3)	180(4.6)
Period of ART start, n (%)					
2006-2009	6417(35.6)	2154(36.7)	1431(40.1)	1683(36.3)	1149(29.2)
2010-2013	7010(38.9)	2306(39.3)	1392(39)	1760(38)	1552(39.4)
2014-2017	4583(25.5)	1409(24)	747(20.9)	1188(25.7)	1239(31.4)
Country, n (%)					
Botswana	1062(5.9)	363(6.2)	94(2.6)	230(5)	375(9.5)
Eswatini	2153(12)	681(11.6)	411(11.5)	597(12.9)	464(11.8)
Lesotho	2831(15.7)	938(16)	465(13.1)	771(16.6)	657(16.7)
Malawi	3750(20.8)	1321(22.5)	843(23.6)	880(19)	706(17.9)
Tanzania	2557(14.2)	923(15.7)	460(12.9)	634(13.7)	540(13.7)
Uganda	5657(31.4)	1643(28)	1297(36.3)	1519(32.8)	1198(30.4)
Outcomes, n (%)					
Active in care	11516(63.9)	3230(55)	2253(63.1)	3248(70.1)	2785(70.7)
Died	1528(8.5)	799(13.6)	224(6.3)	230(5.0)	275(7.0)
Lost to follow-up	1633(9.1)	743(12.7)	362(10.1)	265(5.7)	263(6.7)
Transferred out	3333(18.5)	1097(18.7)	731(20.5)	888(19.2)	617(15.6)

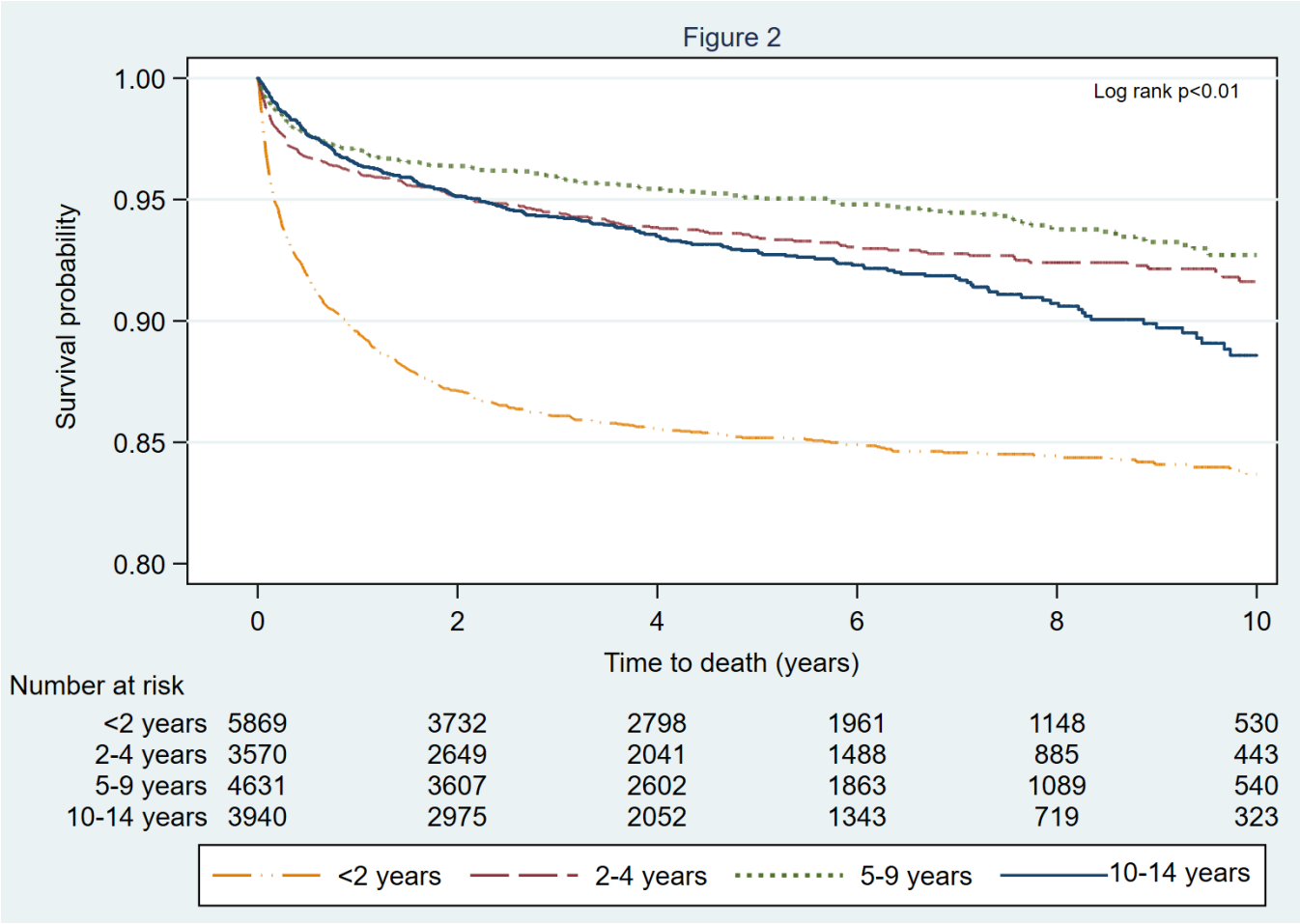


Figure 2: Survival probability after initiating ART by age at initiation among 18,010 children with HIV in BIPAI COEs in six African countries, 2003-2017.

Long-term survival by country and period of ART initiation

Fig 3a and 3b show survival probabilities after initiating ART by country and by year of ART initiation respectively. Overall, there were significant country differences in 10-year survival (Log-rank p<0.01). The 10-year survival probabilities were similar in Botswana, Uganda, and Eswatini, and the survival probabilities in these countries were higher than those in Malawi and Lesotho. Children in Tanzania had not accrued up to 10 years of follow-up; however, at 5-years of follow-up, they had lower survival probability than those in Botswana and Uganda (supplementary table 1). The survival probabilities did not differ by year of ART initiation (Fig 3b and Supplementary Table 1).

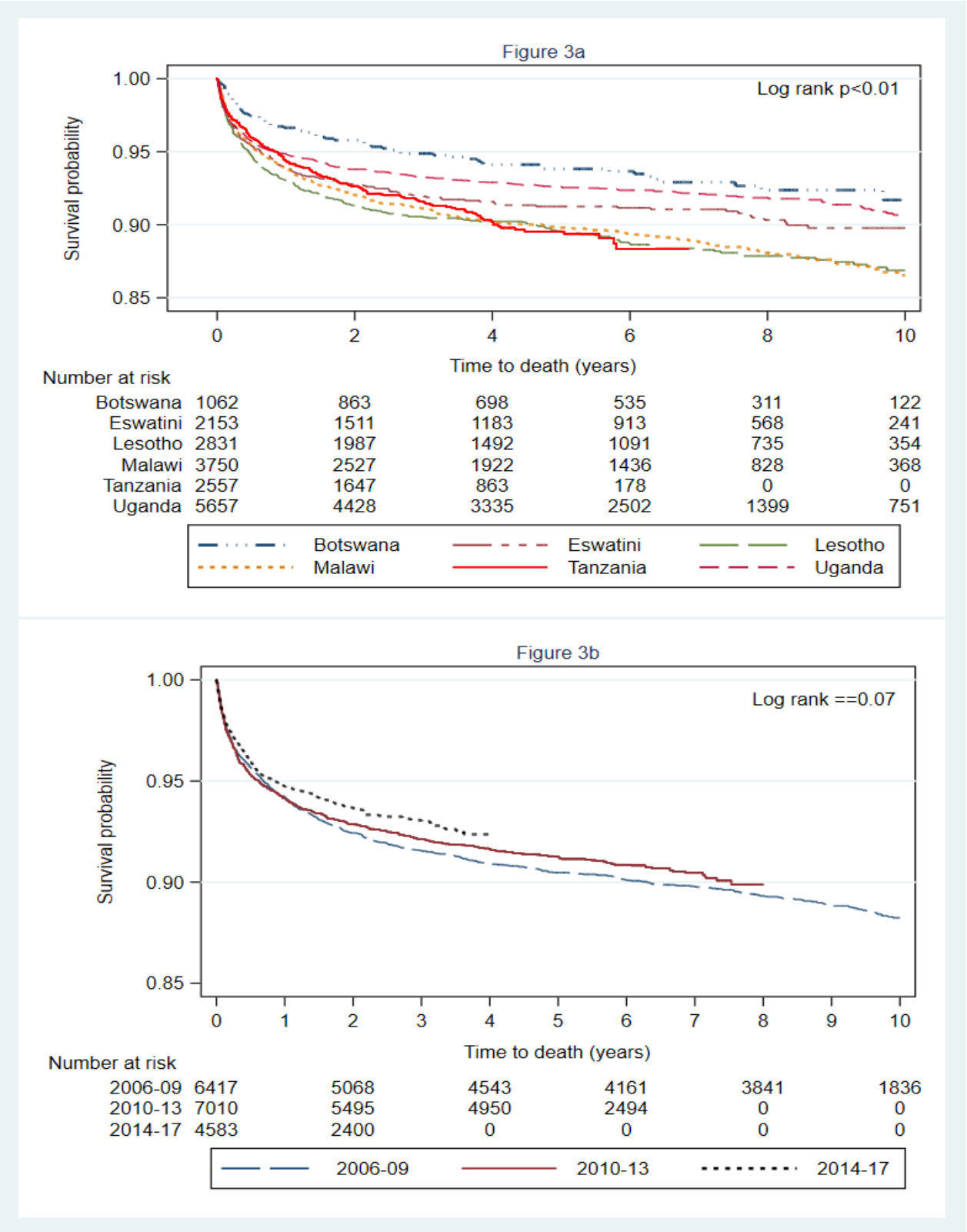


Figure 3: Survival probability after initiating ART by COE and period of initiation among 18,010 children with HIV in BIPAI COE's in six African countries, 2003-2017. *By COE (a) and period of ART initiation (b)*

Factors associated with mortality within six months of ART

In multivariable regression analysis of short-term mortality, the factors associated with a higher risk of death were: being <2 years of age compared to age 10-14 years, stage 3 and stage 4 disease compared to stage 1 or 2, moderate or severe immune suppression compared to no or mild immune suppression, underweight compared to normal weight for age (Table 2). Additionally, compared to Uganda, children who initiated ART in Lesotho had a higher risk of death, while those who initiated in Botswana, Malawi, and Tanzania had a lower risk of death. Children who initiated ART between 2014-2017 had a lower risk of death than those who initiated ART between 2006-2009, and an increase in hemoglobin levels was associated with a lower risk of death. There was no difference in risk between the ART regimens. Sensitivity analysis with complete case analysis and competing risks analysis found similar associations (supplementary table 2)

Factors associated with mortality after between 6-24 month of receiving ART

After six months on ART, age <2 years, time updated stage 3&4 disease stage, moderate or severe immune suppression and underweight continued to be associated with a higher risk of disease. Variables that were not significantly associated with death in the first six months of ART but became significant after six months are baseline age 5-9 years compared to age 10-14 years, PI-based regimen compared to NNRTI-based regimen and initiating ART in 2010-2013 compared to initiating in 2006-2009 (Table 2). Except Malawi where the risk of death remained lower, there was no longer a difference in risk between other sites and Uganda.

Table 2: Risk factors for deaths within the first six months of ART and during 6-24months of ART.

Characteristic	0-6 months, N=18,010						6-24 months·, N=16,289†					
	No of deaths	Mortality rate/ 100 PY	Univariableβ		Adjusted		No of deaths	Mortality rate/ 100 PY	Univariableβ		Adjusted	
			HRδ	95%CI	HRδ	95% CI			HRδ	95%CI	HRδ	95% CI
Age(years)												
10-14	91	4.76	1		1		88	1.77	1		1	
5-9	106	4.75	1.00	0.75, 1.32	1.13	0.85, 1.50	54	0.92	0.52	0.37, 0.73	**0.71**	**0.50, 1.00**
2-4	115	6.76	1.41	1.07, 1.86	1.00	0.76, 1.33	48	1.09	0.62	0.43, 0.88	0.78	0.54, 1.13
<2	471	17.5	3.62	2.9, 4.54	**1.41**	**1.11, 1.79**	233	3.63	2.04	1.6, 2.61	**1.63**	**1.25, 2.13**
WHO clinical stage												
1&2	109	3.30	1		1		96	1.12	1		1	
3	180	6.71	2.02	1.59, 2.56	**1.36**	**1.06, 1.73**	133	1.90	2.4	1.84, 3.13	**1.64**	**1.25, 2.15**
4	464	23.87	7.08	5.75, 8.72	**2.95**	**2.33, 3.73**	171	3.78	6.05	4.7, 7.78	**2.52**	**1.91, 3.32**
Immune suppression level												
None/mild	102	1.97	1		1			0.73	1		1	
Moderate	63	7.01	3.52	2.57, 4.81	**2.64**	**1.90, 3.66**	104	2.07	5.16	3.51, 7.6	**2.75**	**1.9, 3.99**
Severe	426	30.83	15.09	12.16, 18.73	**6.71**	**5.29, 8.52**	46	6.97	10.24	7.43, 14.11	**4.05**	**2.86, 5.72**
Hemoglobin mg/dl			0.65	0.63, 0.67	**0.75**	**0.72, 0.78**	201		0.69	0.66, 0.73	**0.75**	**0.71, 0.79**
Underweight												
None/mild	141	3.34	1		1		98	0.88	1		1	
Moderate	142	7.45	2.22	1.75, 2.8	1.25	0.98, 1.59	78	1.59	2.05	1.53, 2.76	**1.94**	**1.46, 2.59**
Severe	491	21.31	6.25	5.18, 7.54	**1.84**	**1.48, 2.29**	244	4.52	6.85	5.32, 8.84	**4.23**	**3.25, 5.52**
Regimen												
NNRTI_based	618	8.40	1		1		362	1.90	1		1	
PI_based	165	14.01	1.66	1.4, 1.97	0.86	0.71, 1.06	61	2.27	1.17	0.89, 1.54	**0.67**	**0.49, 0.91**
Period of ART start												
2006-2009	276	9.06	1		1		187	2.30	1		1	
2010-2013	324	9.77	1.08	0.92, 1.26	1.17	0.98, 1.39	154	1.76	0.76	0.62, 0.94	**0.75**	**0.59, 0.96**
2014-2017	183	8.42	0.93	0.77, 1.12	**0.77**	**0.62, 0.96**	82	1.69	0.71	0.55, 0.92	**0.67**	**0.49, 0.91**
Country‡												
Uganda	239	8.83	1		1		100	1.39	1		1	
Botswana	27	5.24	0.59	0.4, 0.88	**0.62**	**0.41, 0.94**	16	1.15	0.83	0.49, 1.4	0.62	0.36, 1.07
Eswatini	98	8.41	0.94	0.75, 1.19	1.05	0.82, 1.35	49	2.39	1.38	0.98, 1.95	0.94	0.65, 1.34
Lesotho	148	9.64	1.08	0.86, 1.37	**1.28**	**1.03, 1.59**	85	1.94	1.78	1.33, 2.37	1.21	0.89, 1.63
Malawi	170	11.04	1.25	1.01, 1.53	**0.72**	**0.58, 0.90**	104	2.49	1.72	1.31, 2.26	**0.61**	**0.45, 0.82**
Tanzania	101	9.69	1.09	0.89, 1.32	**0.63**	**0.49, 0.80**	69	2.41	1.7	1.25, 2.31	1.02	0.73, 1.43

¥ PY- person-years; δHR- Hazard ratio; Bold figure show adjusted HR with p<0.05; β TB and sex were significant at univariable analysis and not at multivariable analysis. † Disease stage, immune suppression, underweight and hemoglobin measures were time-updated. ‡ Uganda was selected as a reference because it had the largest frequency.

Supplementary table 1: Kaplan-Meier estimates of survival probabilities % (95% CI) of children with HIV receiving antiretroviral therapy by age group, site and period of ART initiation.

		Time to death from ART initiation			
Characteristic		6 months	2 years	5 years	10 years
Age group					
	<2 years	91.8(91.1-92.5)	87.1(86.2-88.0)	85.2(84.2-86.1)	83.7(82.5-84.8)
	2-4 years	96.7(96.1-97.3)	95.2(94.4-95.8)	93.5(92.5-94.3)	91.6(90.3-92.8)
	4-9 years	97.7(97.2-98.1)	96.4(95.8-96.9)	95.1(94.4-95.7)	92.7(91.5-93.8)
	10-14 years	97.7(97.1-98.1)	95.1(94.4-95.8)	92.9(92.0-93.7)	88.6(86.7-90.2)
Country					
	Botswana	97.4(96.3-98.2)	95.8(94.4-96.9)	93.8(92.1-95.2)	91.7(89.1-93.7)
	Eswatini	95.4(94.4-96.2)	92.7(91.5-93.8)	91.3(89.9-92.5)	89.8(88.1-91.2)
	Lesotho	94.7(93.8-95.5)	91.3(90.2-92.3)	89.6(88.3-90.7)	86.9(85.2-88.4)
	Malawi	95.3(94.6-96.0)	92.0(91.1-92.9)	89.8(88.7-90.8)	86.5(84.9-88.0)
	Tanzania	96.0(95.1-96.7)	92.7(91.5-93.7)	89.5(88.0-90.9)	
	Uganda	95.7(95.2-96.2)	93.8(93.1-94.4)	92.6(91.9-93.3)	90.7(89.6-91.6)
Period of ART initiation					
	2006-2009	95.6(95.1-96.1)	92.4(91.7-93.1)	90.5(89.7-91.2)	88.2(87.3-89.1)
	2010-2013	95.3(94.8-95.8)	92.9(92.2-93.5)	91.3(90.5-91.9)	
	2014-2017	95.9(95.3-96.5)	93.7(92.9-94.4)		

Supplementary table 2: Risk factors for death after complete care analysis and competing risk analysis.

Characteristic		Complete case analysis				Competing risk analysis‡	
		0-6 months N=12332		6-24 month N=7246		0-6 months N=18010	
		aHR$^{\delta}$	95% CI	aHR$^{\delta}$	95% CI	asHR¥	95% CI
Age(years)							
	10-14	1		1		1	
	5-9	1.28	0.91, 1.79	0.80	0.43, 1.51	1.13	0.85, 1.50
	2-4	0.79	0.55, 1.14	1.09	0.59, 2.00	1.00	0.76, 1.32
	<2	**1.42**	**1.06, 1.89**	**1.27**	**0.77, 2.09**	**1.4**	**1.1, 1.78**
WHO clinical stage							
	1&2	1		1		1	
	3	**1.44**	**1.07, 1.95**	1.34	0.82, 2.18	**1.36**	**1.06, 1.73**
	4	**3.18**	**2.38, 4.24**	**2.78**	**1.75, 4.41**	**2.94**	**2.29, 3.77**
Severe immune suppression							
	None/mild	1		1		1	
	Moderate	**2.39**	**1.69, 3.39**	**3.23**	**1.91, 5.45**	**2.62**	**1.88, 3.65**
	Severe	**6.82**	**5.34, 8.7**	**4.92**	**3.18, 7.60**	**6.62**	**5.16, 8.51**
Haemoglobin mg/dl		**0.73**	**0.7, 0.76**	**0.76**	**0.71, 0.83**	**0.75**	**0.72, 0.78**
Underweight							
	None/mild	1		1		1	
	Moderate	**1.1**	0.82, 1.47	1.15	0.70, 1.91	1.25	0.97, 1.61
	Severe	**1.58**	**1.22, 2.04**	**3.13**	**2.01, 4.86**	**1.83**	**1.45, 2.32**
Regimen							
	NNRTI_based	**1**		1		1	
	PI_based	0.8	0.62, 1.04	0.69	0.34, 1.37	0.87	0.7, 1.08
Period of ART start							
	2006-2009	1				1	
	2010-2013	1.17	0.95, 1.45	**0.55**	**0.34, 0.89**	1.17	0.99, 1.39
	2014-2017	0.77	0.57, 1.05	**0.40**	**0.19, 0.83**	**0.78**	**0.63, 0.97**
Country							
	Uganda	1				1	
	Botswana	0.74	0.42, 1.32	0.34	0.08, 1.49	**0.64**	**0.42, 0.97**
	Eswatini	1.09	0.81, 1.46	0.62	0.31, 1.24	1.07	0.83, 1.36
	Lesotho	**1.36**	**1.05, 1.76**	0.82	0.44, 1.52	**1.31**	**1.05, 1.62**
	Malawi	0.78	0.57, 1.05	0.82	0.44, 1.54	**0.73**	**0.58, 0.92**
	Tanzania	**0.42**	**0.3, 0.58**	0.89	0.47, 1.66	**0.62**	**0.49, 0.80**

$^{\delta}$ aHR-adjusted hazard ratio; ¥sHR- sub distributional hazard ratio; ‡ Loss to follow-up was considered a competing risk.

DISCUSSION

In this study, we report age-specific 10-year survival and factors associated with early mortality in a cohort of 18,010 children with HIV, who initiated ART between 2006 and 2017 in BIPAI clinics in six countries in Eastern and Southern Africa. We report three findings. First, the 10-year survival probability of children living with HIV on ART was good (88.9%); however, children aged <2 years at baseline had poorer survival than older children, and this persisted beyond the first six months on ART. Second, mortality was highest in the first six months but declined after that. Lastly, advanced disease stage, severe immune suppression and underweight were associated with increased risk of early mortality, but mortality risk was lower in children who initiated ART after 2010 compared to those initiated between 2006 and 2009. Our findings have important implications for programs implementing pediatric HIV care. The good long-term survival is encouraging and should motivate early testing and treatment initiation in children. Our findings also re-emphasize the need for early infant diagnosis; early treatment initiation and close monitoring during the first six months of therapy as critical measures to reduce mortality of children with HIV.

The overall 10-year survival probably in this study is similar to those reported in other studies in sub-Saharan Africa [15, 24]; however, they are lower than those reported in high income countries [11, 12]. The differences in survival are likely due to differences in quality of care notably better patient monitoring and treatment regimens. We found children < 2 years had the lowest 10-year survival probability (83%) and the risk of early death was higher in this age group compared to older children (figure 2 &supplementary table 1). Poor survival in children <2 years compared to older children has been reported previously [1, 3, 15, 24-33]. The poor survival in these children may be attributed to rapid disease progression in infancy [34, 35], while higher survival in

older children may be attributed to survival bias. The children who initiated ART at older ages are those who had survived through infancy without receiving ART, and some may be "long-term survivors" [36-38].

Half of the deaths in our study occurred during the first 6 months on ART [mortality rate 9.17 (95% CI: 8.55-9.84) deaths per 100 PY]. In addition to age <2 years, the other factors associated with a higher risk of death within the first six months were WHO stage 3 or 4, severe immune suppression and underweight, which are all markers of severe HIV disease. These findings imply these children initiated ART late. These findings, which have been reported in other studies [1, 3, 15, 25-30], highlight two important needs that should be addressed in order to mitigate early mortality in children with HIV. First, there is a need for continued efforts to diagnose and treat HIV in children early. Early diagnosis and treatment (within three months of birth) reduce mortality in infants by about 75% [39]. Access to early testing is still a challenge in Eastern and Southern Africa. In 2017, only half of the HIV-exposed children in the study countries received a virological HIV test within 2-months of birth [40]. Improving retention of mother-infant pairs in the postnatal period, integrating early infant diagnosis in child survival platforms like immunization programs and expanding access to the point of care testing could improve early testing. The current WHO treatment guidelines, which recommend initiating ART upon diagnosis irrespective of disease severity [5], provide an opportunity to initiate treatment early. Early treatment will only improve survival if the children are diagnosed early.

In addition to early infant diagnosis, the second need is for close monitoring of children during the first 6-month period on ART and treating opportunistic infections. Although the WHO recently provided guidance for treating patients with advanced HIV disease [21], specific guidance for children under 5-year with advanced HIV disease was lacking. Updated data on frequent

causes of morbidity and deaths among children with advanced HIV in RLS are needed and intervention packages to reduce early mortality in these children may need to updated or developed.

Encouragingly, we found that during the first two years on ART, mortality decreased with increasing calendar period of ART initiation. In the multivariable analysis, the risk of death in the first six months of ART was similar in children who initiated ART between 2010 and 2013 compared to those initiated in 2006-2017, but lower in those who initiated ART between 2014 and 2017. Among children who survived beyond 6 months, the risk of death was lower in those who initiated ART in 2010 and beyond compared to those who initiated ART between 2006-2009 (table 2). This finding is unlikely due to better regimens and current guideline changes because regimens and disease severity characteristics were controlled for in the analysis. The finding may, therefore, represent a general improvement in care for children as health workers become better trained and more confident treating children with HIV, and use of better monitoring strategies, e.g., using viral load which has been associated with better survival. Since 2014, the studies sites have used viral load measurements to monitor treatment progress in children. Additionally, the reduced risk of death after 2010 may also be due to the general temporal improvements in survival in all children observed in the study countries [41].

The major strength of our study is that it is one of the few multi-country studies in sub-Saharan African that provides age-specific 10-year survival estimates of children receiving ART. This allowed us to evaluate the impact of routine treatment programs on the survival of children with HIV. Also, we were able to examine calendar periods that cover the most recent treatment guidelines.

Our study also has several limitations. First, up to 9% of our patients were LTFU, and there is a possibility of informative censoring due to loss to follow-up which would lead to underestimation of mortality. However, our sensitivity analysis treating loss to follow-up as a competing risk found similar results showing that our findings are robust. Second, we do not report causes of death; this is unfortunate as it would be helpful to guide intervention to reduce mortality. In RLS, causes of death are not well documented. Third, we used CDC growth standards to determine WAZ scores in children 10-14 years; this may have resulted in an overestimation of underweight in these children since the CDC growth standards are mainly based on measurement of growth in children in high-income countries. Lastly, our study was conducted in COEs, which have higher standards of care than the general population; thus, our mortality estimates may underestimate the mortality rates in children on ART.

Despite these limitations, our study findings are important for improving survival in children. The finding that long-term survival in children is good should motivate the caretakers of at-risk children to test them for HIV and to start ART immediately upon diagnosis. Prognostic information is important for developing interventions to reduce early mortality. In addition, the data on age-specific long term survival on ART could be used to model pediatric HIV epidemiological estimates and life expectancy in children receiving ART. Lastly, our findings will also provide a benchmark against which future intervention and guidelines will be measured.

CONCLUSION

Our study shows that overall 10-year survival in children receiving ART is good but varies by age group. Mortality rates are highest in children aged < 2years and during the first six months of ART. Disease severity characteristics were associated with a higher risk of early mortality, and children who initiated ART after 2010 had a lower risk of mortality than those

who initiated before. In order to improve survival in children with HIV receiving ART, problems of late diagnosis and late treatment initiation should be addressed and close patient monitoring in the first six months of care should be emphasized.

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JOURNAL ARTICLE 3: Rapid antiretroviral therapy initiation and the risk of mortality and loss to follow-up in children with HIV

Suggested Journal: Journal of Acquired Immune Deficiency Syndrome (JAIDS)

ABSTRACT

Introduction

Although rapid ART initiation (initiating ART within 7-days of diagnosis) is associated with better survival, retention and viral suppression in adults, data on these benefits in children are limited. We examined the association between rapid ART initiation (same-day or 2-7 days versus 8-90 days from entry into care) in children and 24-month all-cause mortality or loss to follow-up (LTFU).

Methods

We retrospectively analyzed data of HIV-infected children who initiated ART between 2014-2017 at seven Baylor International Pediatric AIDS Initiative clinics in Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda. We defined LTFU as having a gap of 90 days between the next clinic appointment and the database closure date (December 31, 2017). Follow-up time accrued from the ART initiation date to the earliest of LTFU, death, transfer out, 24 months of follow-up or the database closure date. We assessed the association between rapid ART initiation, and mortality or LTFU using the Fine and Gray's sub-distribution hazard regression for competing risks, adjusting for known risk factors of mortality and LTFU.

Results

Of the 3,299 participants, 1,516 (46%) initiated ART within 8-90 days of entry into care, 1004 (20%) initiated ART within 2-7 days and 872 (24%) initiated ART on the same-day. Forty percent of the children were aged <2 years, and half were girls. Overall, 254 (7.7%) died, 306 (9.3%) children were LTFU, 315 (9.6%) transferred care to another clinic and 2424 (73.5%) remained in care. The risk of mortality was similar between children who initiated ART on the same-day [adjusted sub distributional hazard risk (aSHR) =1.10, 95% CI 0.79, 1.75] and those who initiated within 2-7 days (aSHR=1.05, 95% CI 0.77, 1.43) compared to those who initiated within 8-90 days. The risk of LTFU was higher in children who initiated

ART on the same day (aSHR=1.86, 95% CI 1.39, 2.49) and those who initiated within 2-7 days (aSHR=1.83, 95% CI 1.38, 2.43) compared to those who initiated within 8-90 days.

Conclusion

Rapid ART initiation in children is associated with an increased risk of LTFU but not mortality. This data suggest that rapid ART initiation in children is feasible but loss to follow-up should be addressed.

INTRODUCTION

In 2014, the Joint United Nations Program on HIV/AIDS (UNAIDS) set ambitious targets described as "95-95-95" targets to end AIDS by 2030 [1]. These targets are that 95% of people living with HIV know their HIV status, 95% of those diagnosed with HIV initiate and sustain ART and 95% of those on ART achieve and maintain viral suppression. To attain these targets, children diagnosed with HIV must be linked to HIV care, promptly initiated on ART and retained in care. However, 20% of children with HIV are lost to follow up between diagnosis and ART initiation [2]. After initiating ART, mortality ranges from 4.3-29% [3-6] and loss to follow-up (LTFU) ranges from 2-39% [6-10]. These high losses to follow-up and mortality, if not addressed, can preclude attainment of the 95-95-95 goals for children by 2030.

As a strategy to reduce loss to follow-up and mortality in people living with HIV, the World Health Organization in 2017 recommended initiating ART in all people with HIV within 7-days (including same-day initiation in people who are ready) upon diagnosis and clinical assessment.[11]. This accelerated ART initiation also called rapid ART initiation. This recommendation for rapid ART initiation followed a systematic review of evidence from trials in adults that showed rapid ART initiation was associated with an increased likelihood of starting ART, reduced mortality, and better viral suppression and retention in care as compared to delayed initiation.[12]

Although the WHO recommended rapid ART initiation in children as well, data on the effect of rapid ART initiation on outcomes of children were limited. Two trials conducted among hospitalized children showed no difference in mortality in children who initiated ART rapidly versus those on delayed initiation [13, 14]. These studies do not include children who are not severely ill, and they do not examine if rapid ART initiation is associated with loss to follow-up, yet, observational studies in adults show an increased risk of being lost to follow-up after rapid ART initiation compared to delayed ART initiation [15, 16].

Given the paucity of data on this topic in children, we examined whether rapid ART initiation was associated with mortality and loss to follow-up in a cohort of children with HIV who initiated ART between 2014 and 2017 at Baylor International Pediatric AIDS Initiative (BIPAI) centers of excellence (COE) in six African countries.

METHODS

Study design

We conducted a retrospective cohort study using electronic medical records of children with HIV, who initiated ART at seven BIPAI COEs in Botswana, Eswatini, Lesotho, Malawi, Tanzania, and Uganda. The study was approved by ethics committees and institutional review boards in each country, Baylor College of Medicine, and University of Texas Health Science Centre at Houston.

Study setting and treatment program.

The BIPAI COEs, which were started in partnership with respective governments, provide free HIV/AIDS treatment and prevention services to children and adolescents. In 2014 and June 2016, all the COEs except Uganda implemented 2013 WHO guidelines which recommended initiating ART in all children aged <5 years irrespective of disease severity. Children aged 5-14 years were initiated if they have stage 3 or 4 disease or CD4 count <500 cells/mm^3. After June 2016, they updated the guidelines upon 2015 WHO recommendations to initiate ART in all children <15 years irrespective of disease severity. Uganda implemented the guidelines to initiate ART in all children <15 years irrespective of disease severity from 2014.

At the COEs, caretakers of children receive pre-ART adherence counseling before initiating the children on ART. Older children and adolescents, who are disclosed to and know their HIV status, usually participate in the counseling session. Those who are ready to initiate ART receive medication on the same day, while those who are not ready are given an appointment within seven days for another session and are

then initiated if ready. If the client is not ready after 7-days, the next appointment is given within the next month on a mutually agreed date. Patients who do not return for appointments are tracked. After ART initiation, the children are reviewed at two weeks, at one month and after that 3-monthly if they are medically stable. Shorter appointments are given if medically indicated or if more psychosocial support and counseling are required.

Study participants and data collection

We included ART-naive HIV-infected children aged <15 years who entered HIV care at the study sites between January 2014 and 2017 and initiated ART within 90 days of enrollment. Ninety days was the median time to ART initiation observed among patients diagnosed at enrollment in a global study of access to ART in children [2]. However, we also assumed that if children were eligible at enrollment, ART should be initiated at most within 90-days. We excluded children who initiated ART less than 6-months from the database closure date (December 31, 2017). The individual patient data were pooled electronically, anonymized and transferred to the research team for cleaning and management.

Variables and definitions

Exposure: The exposure was the timing of ART initiation, which we categorized into same-day initiation, 2-7 days and 8-90 days. ART initiation on the same-day and within 2-7 days are defined by WHO as rapid ART initiation [11]. In our analysis, the reference group for comparison was those who initiated ART within 8-90 days.

Outcome: The outcomes of the study were all-cause mortality and loss to follow-up (LTFU). LTFU was defined as having a gap of 90 days between the next clinic appointment and the database closure date (December 31, 2017). The date of LTFU was the date the patient chart was closed in the EMR, and if the chart was not closed, the patient was censored 90 days after the last scheduled appointment. Censoring events were transferred out and active in care. The date of death and transfer out were the dates recorded in the EMR, and if missing, the date the chart was closed in the EMR was used. Children were considered

active in care if none of the other outcomes had occurred and they were assigned the date of the last visit as the outcome date.

Other covariates: Other covariates considered were age, sex, country World Bank income category (middle income vs. low income), weight for age Z-scores (WAZ), TB diagnosis, WHO clinical disease stage (WHO stage) and immune suppression level and period of initiation (2014-2015 versus 2015-2016). The WAZ was computed from the weight taken on the ART start date. If weights were missing, weight taken ± 1month from ART start date was used. WAZ for children aged < 10 years were computed using the WHO child growth standards [17, 18] and for children 10-14 years using the Centers for Diseases Control and Prevention (CDC) growth standards [19]. The CDC growth standards were used for children aged 10-14 years because this measure was not available in the WHO growth standards. CD4 counts or CD4 percentage cut were categorized into immune suppression level (no/mild, moderate or severe) for age according to the WHO classification [11, 20]. The year of initiation was categorized as 2014-2015 and 2016-2017.

Data analysis

Baseline characteristics at ART initiation were summarized using frequencies and proportions for categorical variables, and medians and interquartile ranges (IQR) for continuous variables, stratified by the timing of ART initiation. We considered death and LTFU as competing risks events and estimated the 24-month cumulative incidence probabilities by the timing of ART initiation using competing risks survival analysis[21-23]. Follow-up time accrued from the ART initiation date to the earliest of LTFU, death, transfer out, 24 months of follow-up or the database closure date (December 31, 2017). We assessed the association between rapid ART initiation and 24-months' mortality and LTFU using the Fine and Gray's sub-distribution hazard regression model for competing risks adjusting for covariates[21]. Covariates were selected using stepwise regression setting the criteria for a variable to enter and stay in the model at p=0.15 and p=0.05, respectively. Known risk factors of mortality and LTFU were purposefully included in the mortality and LTFU analysis

respectively. We imputed missing CD4, WHO clinical stage, WAZ, and hemoglobin values using multiple imputation by chained equations (MICE), using 20 cycles [24, 25].

RESULTS

Characteristics at study participants at ART initiation

A total of 5,919 children enrolled in HIV care during the study period, of whom 5,483 initiated ART. Of these, we excluded 18 children who were ≥15 years at ART initiation, 1,426 who were not ART naïve at enrollment, 397 who initiated ART <6 months before the end of the observation period, 213 who initiated ART after 90 days and 107 had only one medical visit. Patients who initiated ART after 90 days had less advanced HIV/AIDS than those who initiated ART in less than 90-days (data not shown). The available sample size after all exclusions was 3,299 participants (Figure 1). Among the 107 children had only one visit, of whom 93 (86.9%) were initiated on the same-day, 8 (7.5%) within 2-7 days and six (5.6%) within 8-90 days. Upon tracking, 47 (44%) had died, five (4.6%) had self-transferred out, and 55 (51.6%) were lost to follow-up (results not shown). Those who died, died within 5-days of initiating ART.

Table 1 describes the characteristics of the study participants stratified by the timing of ART initiation. Of the 3,299 participants, the majority 1,516 (46%) initiated ART within 8-90 days of entry into care, 1004 (20%) initiated ART within 2-7 days and 872 (24%) initiated ART on the same-day they enrolled into care. Forty percent of the children were aged <2 years, half were girls and the majority were from low-income countries. WHO clinical stage was similar across the strata with nearly equal distribution of children with stage 1/2 and stage 4 disease. About 23.8% of patients had missing immune suppression (CD4) data. The proportion of missing data was highest in those who initiated ART on the same day (40.7%). This is no surprise since the guidelines in 2013 recommended immediate ART for all children <5 years and in 2015, all children <15 years irrespective of CD4 count, so pre-ART CD4 tests were no longer mandatory.

During 57,153 person-months, 254 (7.7%) died, 306 (9.3%) children were LTFU, 315 (9.6%) transferred care to another clinic and 2424 (73.5%) remained in care.

Fig 1. Flow diagram of the inclusion criteria of the children with aged <15 years in the study and outcomes in each stratum of ART.

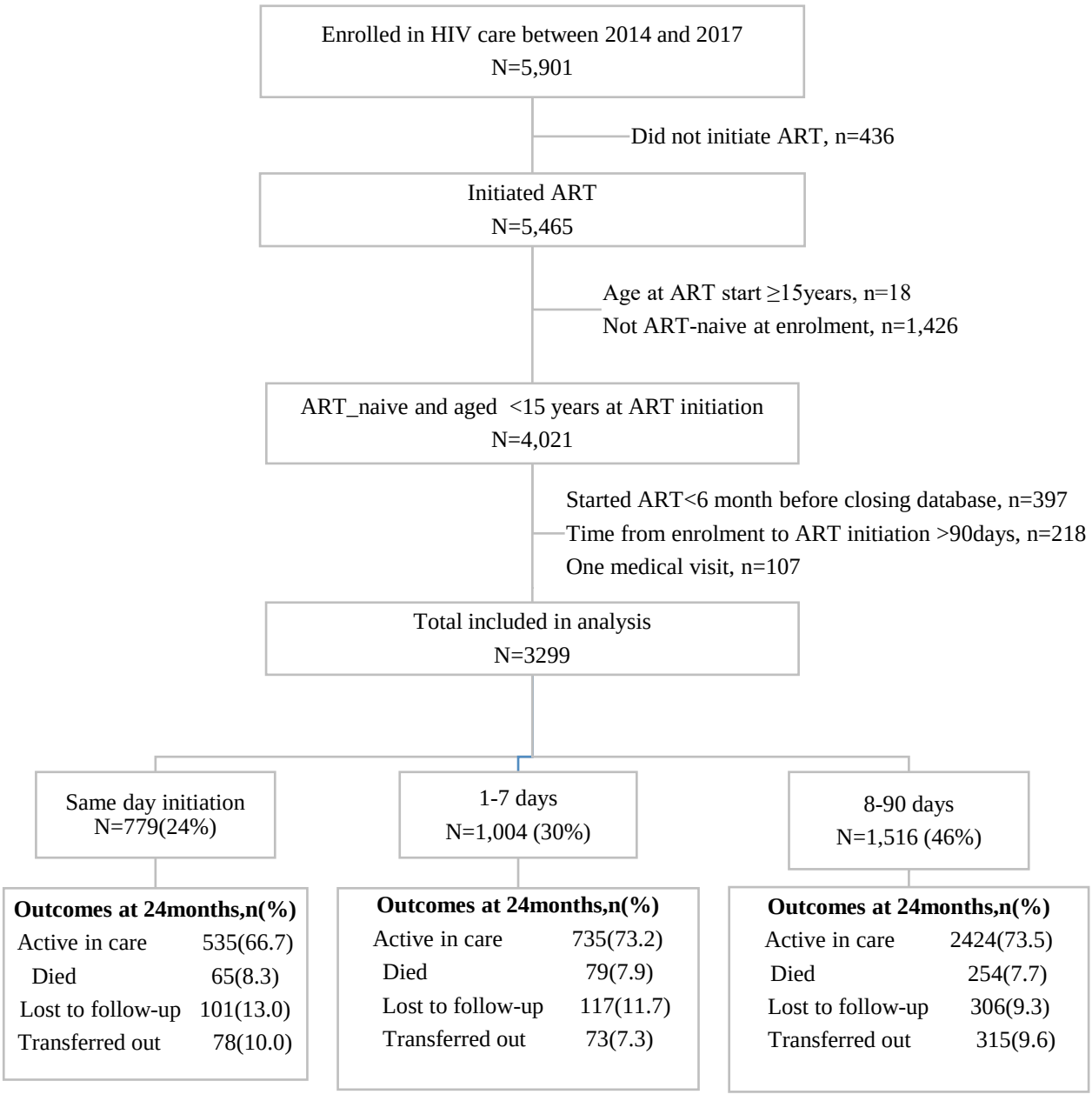

Table 1: Baseline characteristics of participants at ART initiation.

Characteristic	same-day initiation N=779	2-7 days N=1004	8-90 days N=1516	Total N=3299
Age n (%)				
<2 year	369(47.4)	347(34.6)	597(39.4)	1313(39.8)
2-4 years	138(17.7)	253(25.2)	285(18.8)	676(20.5)
5-9 years	159(20.4)	246(24.5)	309(20.4)	714(21.6)
10-14 years	113(14.5)	158(15.7)	325(21.4)	596(18.1)
Sex, n (%)				
Female	415(53.3)	523(52.1)	754(49.7)	1692(51.3)
Male	364(46.7)	481(47.9)	762(50.3)	1607(48.7)
WHO clinical stage, n (%)				
1&2	285(36.6)	367(36.6)	597(39.4)	1249(37.9)
3	142(18.2)	197(19.6)	363(23.9)	702(21.3)
4	286(36.7)	436(43.4)	540(35.6)	1262(38.2)
missing	66(8.5)	4(0.4)	16(1.1)	86(2.6)
Haemoglobin(mg/dl) median(IQR)	10.7(9.3-11.9)	10.9(9.5-12)	10.8(9.5-12)	10.8(9.4-12)
Immune suppression, n (%)				
None/mild	246(31.6)	509(50.7)	714(47.1)	1469(44.5)
Advanced	82(10.5)	93(9.3)	198(13.1)	373(11.3)
Severe	134(17.2)	219(21.8)	320(21.1)	673(20.4)
missing	317(40.7)	183(18.2)	284(18.7)	784(23.8)
Underweight, n (%)				
None/mild	328(42.1)	450(44.8)	715(47.2)	1493(45.3)
mod	156(20)	239(23.8)	319(21)	714(21.6)
Severe	292(37.5)	314(31.3)	482(31.8)	1088(33)
missing	3(0.4)	1(0.1)	0(0)	4(0.1)
ART regimen, n (%)				
NNRTI based	443(56.9)	706(70.3)	1013(66.8)	2162(65.5)
PI- based/other	336(43.1)	298(29.7)	503(33.2)	1137(34.5)
Period of ART start				
2014-2015	344(44.2)	666(66.3)	1019(67.2)	2029(61.5)
2016-2017	435(55.8)	338(33.7)	497(32.8)	1270(38.5)
WB Income level				
Middle income	122(5.7)	57(5.7)	535(35.3)	714(21.6)
Low income	657(94.3)	947(94.3)	981(64.7)	2585(78.4)

§ ART- antiretroviral therapy ‡ WB- World Bank

Timing of ART initiation and the risk of mortality and loss to follow-up

There was a difference in risk of mortality between rapid ART initiation and delayed initiation; however, the rapid ART initiation was associated with a higher risk of LTFU than delayed initiation. There was no difference in the 24-months cumulative incidence (CI) of mortality by timing of ART: same day initiation CI=9.9%, 95%CI 7.7%, 12.5%); 2-7 days CI=8.3%, 95% CI 6.7%, 10.2%, and 8-90 days CI=7.9%, 95% CI 6.5%, 9.4%; $p<0.4$. The 24-month risk of mortality was similar between those who initiated ART on the same day or within 2-7 days compared to those who initiated ART within 8-90 days of entering care after adjusting for other risk factors (table 2).

The 24-months cumulative incidence of LTFU was higher in children initiated on the same-day of entering care (16.3%, 95% CI 13.4%-19.5%) and those initiated within 2-7 days (13.3%, 95% CI 11.1%-15.7%) compared to those initiated within 8-90 days (6.8%, 95% CI 5.5%-8.3%), $p<0.001$ (Figure 1b). The adjusted hazard risk of LTFU was higher in children initiated on the same-day and in those initiated within 2-7 days compared to those initiated within 8-90 days (table 2). Compared to children initiated on ART within 8-90 days, the risk of LTFU in those initiated on the same-day was 1.86 times higher (aSHR=1.86, 95% CI 1.39, 2.49) and the risk in those initiated within 2-7 days was 1.83 times higher (aSHR=1.83, 95% CI 1.38, 2.43).

Figure 2a

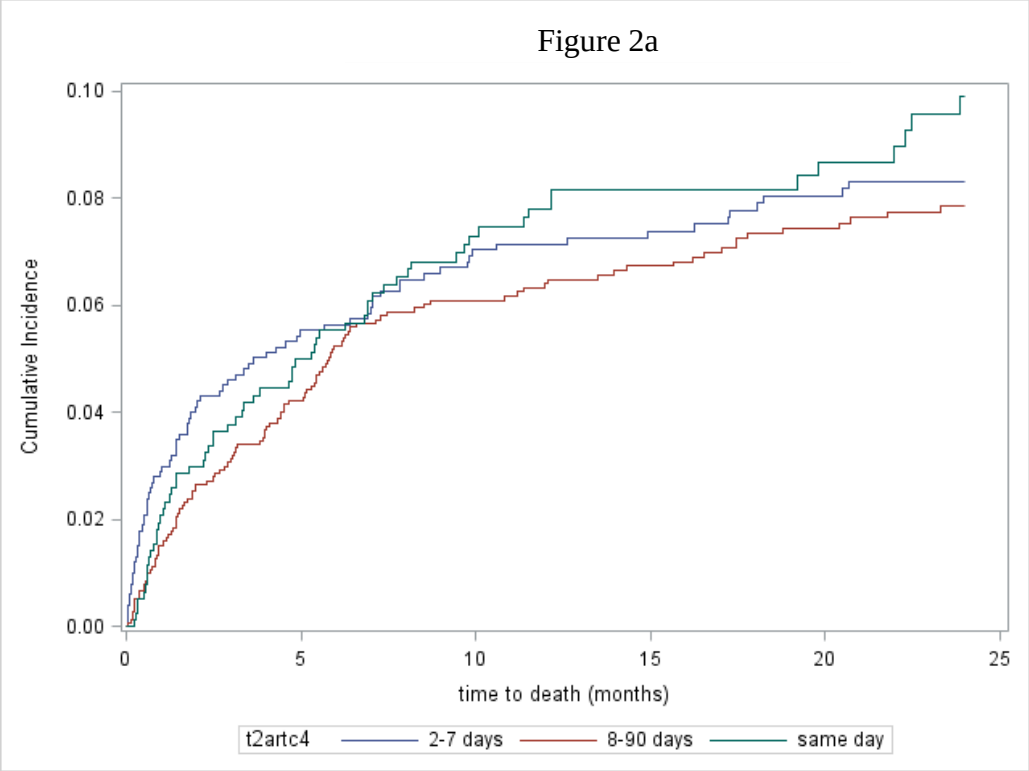

Figure 2b

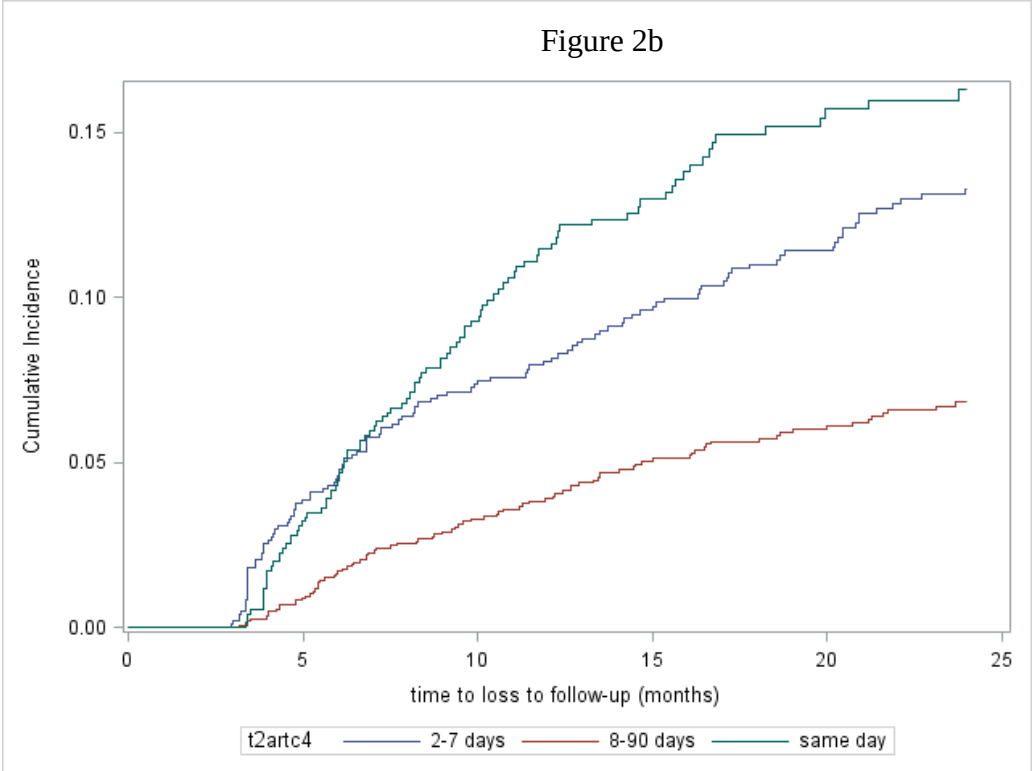

Figure 2: The cumulative incidence of mortality (figure 1a) and loss to follow-up (figure 1b), by the timing of ART initiation among HIV infected children initiated on ART between 2014-2017 at BIPAI COEs in 6 African countries

Table 2: Unadjusted and Adjusted all-cause mortality and loss to follow-up sub-distributional hazard ratios for the first two years of antiretroviral therapy, by the timing of ART.

Timing of ART	Events (n/N)	CIF (%)	95%CI	Unadjusted		Adjusted[§]	
				sHR	95%CI	sHR	95% CI
Mortality							
8-90 days	110/	7.85	6.5, 9.35	1		1	
2-7 days	79/	8.32	6.67, 10.2	1.09	0.81, 1.45	1.05	0.77, 1.43
same-day	65/	9.91	7.67, 12.49	1.21	0.89, 1.65	1.10	0.79, 1.54
Loss to follow-up all children							
8-90 days	88/	6.83	5.52, 8.31	1		1	
2-7 days	117/	13.29	11.12, 15.66	**2.05**	**1.56, 2.71**	**1.83**	**1.38, 2.43**
same-day	101/	16.32	13.43, 19.47	**2.60**	**1.95, 3.45**	**1.86**	**1.39, 2.49**

[§] Adjusted for age, immune suppressions, hemoglobin level, period of ART initiation and country income level. WHO clinical stage was adjusted for in mortality analysis only; ‡ Sensitivity analysis was conducted among patients who had 2 or more visits (N=3299). CIF- cumulative incidence function

DISCUSSION

In this study of 3,299 HIV-infected children aged <15 years who initiated ART between 2014 and 2017 at BIPAI COEs in 6 African countries, we found that in the first 24-months of ART, rapid ART initiation was associated with higher loss to follow-up but was not associated with mortality. Given the need to initiate ART early in children, our findings suggest that rapid ART initiation could be implemented without impacting mortality of children, but loss to follow-up should be addressed

We found that rapid ART initiation (same-day and within 2-7 days) was associated with higher LTFU compared to initiation within 8-90 days even after excluding children who had only one visit after initiating ART. Similar findings have been reported in observational studies among pregnant women with HIV who initiated ART on the same day as diagnosis [15, 16]. In contrast, our previous study in public health facilities in Uganda found no difference in retention among children initiated on the same day and those in whom ART was delayed [26]. However, our previous study was underpowered to detect a difference in retention between the groups; thus, the finding was inconclusive. Although reasons why children who initiated ART on the same-day drop out of care are not well understood, a plausible reason is that the

caregivers of children initiated on the same-day were not ready but chose to accept either because it was offered or because they felt pressured by providers to start, and they dropped-off after starting. Lack of readiness to start and feeling pressured by providers to start ART on the same day has been reported as a reason for dropping off from care among adults [16, 27, 28]. Caretakers of children may require time to reflect on the HIV-diagnosis in the child, the implications of life-long treatment and the need to disclose to their partner if they have not.

We did not find an association between rapid ART initiation and mortality. This finding confirms findings from previous clinical trials conducted among hospitalized children [14, 29]. Although these trials and our study report no association between rapid ART initiation and mortality, we found much lower mortality (9.9%) among children who initiated ART on the same-day compared to the mortality among children who initiated ART within 48hrs in the Kenyan trial (23%). This difference is because the Kenyan study was conducted among Hospitalized children while ours was among a combination of both ill and relatively healthy children. Although, the purpose for immediate ART initiation is to maximize benefits of ART in children, not observing higher mortality in the children who initiated ART within a week is a reassurance that it does not harm. Additional, half of the children initiated ART within a week, meaning that it is acceptable and is feasible to implement without. Other benefits of same-day initiation observed in clinical trials in adults that should be investigated in children include reduced time to viral suppression and reduce pre-ART loss to follow-up. [30-32]

We excluded children who had one visit after initiating ART on the assumption that they never established care. On further analysis, we found these children had higher odds of having advanced disease and those who died, died within 5-days of initiating therapy. Although we could not confirm, it is possible that these children were ill and possibility hospitalized. It is also possible that they would have died even if ART were not initiated. The WHO guidelines recommend that in ill children, management of acute

conditions should be prioritized over ART initiation [11]. More work, however, is required to understand which children do not return to care after rapid initiation and why they do not return into care. Theory-based should be used to understand the underlying determinant of loss to follow up and develop evidence-based interventions to reduce loss to follow-up. Such approaches include intervention-mapping approach [33]

Several limitations need to be considered when interpreting our findings. First, patients reported as lost to follow-up may have died and were misclassified as LTFU. Our findings may, therefore, underestimate mortality. However, we are not certain if this bias would be differential or non-differential. Second, our analysis of LTFU did not control for structural and psychosocial determinants of loss to follow-up like the distance traveled to the clinic, and hence there is potential for residual confounding; however, we cannot determine the direction. Third, we excluded patients who initiated ART after 90 days of enrolling into care. These patients were relatively healthy at ART start, and by excluding them from the reference group, we may have overestimated mortality in the patients who delayed ART initiation, thus biasing our mortality estimates towards the null. However, this group represented only 6% of the population, previous global analysis of time to ART found a median initiation time to ART of 1 month [2] and as programs implement ART guidelines [34], time to ART will be shorter; thus, our cut off time of 90 days is reasonable. Lastly, we excluded patients who had only one visit. These patients had higher odds of advanced disease; most had been initiated on the same day and those who died, died within five days. We may have underestimated mortality among those who initiated ART on the same day; however, given that most of these patients died within five days, we assumed they had not established HIV care

Notwithstanding the limitations, findings from our study, which is conducted in a programmatic setting, have important implications for the implementation of the universal ART and rapid ART initiation guidelines in children. These findings suggest that in programmatic settings, it is feasible to implement rapid ART initiation in children; however, loss to follow should be addressed. To attain better outcomes in

children during the implementation of rapid ART initiation, ART initiation protocols that incorporate rapid diagnostic assessment, readiness assessment, and retention strategies should be developed and tested in programmatic settings. Because in untreated children HIV progression is fast and mortality is high [35-37], care should be taken not to over-delay ART in children and miss the benefits of ART. If the rapid ART initiation guidelines are implemented without approaches to reduced mortality and loss to follow-up, attaining the 95-95-95 goals for children in 2030 may be elusive.

CONCLUSION

Our study shows that in the first 24-months of ART, rapid ART initiation is associated with worse loss to follow-up but did not affect mortality in children aged <15 years. Our findings suggest that rapid ART initiation in children is feasible, but loss to follow-up needs to be addressed. More research is required to develop approaches and models for implementing rapid ART initiation in children while maintaining good outcomes for children.

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CONCLUSIONS

In these three studies conducted among HIV infected children (0-14 years) who initiated ART between 2003-2017 at seven Baylor International Pediatric AIDS Initiative centers of excellence in 6 Eastern and Southern African countries, we have described age- and site-specific trends in advanced disease at ART initiation. We also described 10-years survival and risk factors of early mortality and examined the association between rapid ART initiation and outcomes of HIV infected.

We found that the between 2003-2017, trends proportion of children with advanced HIV disease at ART initiation varied age group and country. The proportion declined in children aged 5-14 years, remained the same in those aged <2 years and increased slightly in those age 2-4 years. We also found that over time children initiating ART in southern Africa sites were older and less severely ill, while those in Eastern Africa sites were younger and more severely ill. In addition, at the end of the observation period (2016-2017), most children initiated ART within one week of entry into care, but a substantial proportion initiated ART with advanced disease. Our study also found that about 88.9% of children with HIV will be alive ten years after starting ART, but survival was lower in children < 2years (83%). We also established that 50% of the deaths were within six months of starting therapy and that young age (<2 years), advanced HIV disease and being underweight were associated with advanced HIV disease. Lastly, we found that rapid ART initiation in children was independently associated with a higher risk of loss to follow-up after 24-months of ART but was not associated with mortality.

Our findings have important implications for pediatric HIV prevention, care and treatment programs. First, our findings re-emphasize the need for more efforts to diagnose and initiate children on ART early, and the need to closely monitor children during the first 6-months of

ART as measures to reduce mortality in children with HIV. Our finding that long-term survival in children is good should motivate the caretakers of at-risk children to test them for HIV and to start ART immediately upon diagnosis. Additionally, the data on age-specific long-term survival on ART could be used to model pediatric HIV epidemiological estimates and life expectancy in children receiving ART. Prognostic information can guide the development of interventions to reduce early mortality. Lastly, our study shows that rapid ART initiation can be implemented in children, but the high loss to follow-up should be addressed.

As mentioned in our papers, the strength of our studies was the use of large dataset from multiple countries and spanning 5-periods of implementation of different WHO guidelines. This enable used to compared trends and outcomes across countries and different guideline implementation periods. In addition, our study also examines age-specific trends in advanced disease and long-term survival, and this enabled us to show how pediatric HIV program implementation and guidelines have differentially affected outcomes of different age groups of children. Our studies also had weaknesses that should be considered when interpreting our findings. First, the generalizability of our findings should be treated with caution because our study sites are well resourced, better staffed and likely to have a higher quality of care than public health facilities. However, in some countries like Botswana, our the study site provide care to nearly a third of all children in the country, and this enhances generalizability. Second, as with most observational data, we had missing data for important variables; however, to avoid loss to information, we imputed missing values. Third, in some of our analysis, there was potential for informative censoring due to loss to follow-up, but we conducted sensitivity analysis in one analysis that showed our results were robust and used competing risks analysis in other to address informative censoring. Lastly, in our analysis of the association between rapid

ART initiation and loss to follow-up, we did not adjust to structural and psychosocial determinants of loss to follow-up, which could have led to residual confounding.

Future studies are required to identify interventions to reduce early mortality and loss to follow-up in children with HIV especially in the current era of "treat all" guidelines and rapid ART initiation. Such interventions should be theory-based and should focus on identifying and addressing health systems changes and individual behaviors required to improve implementation of pediatric HIV programs and improving outcomes. While the specific focus should be on pediatric HIV, the interventions should have far-reaching benefits, for example, improving systems for delivery of child survival interventions as a whole.

In conclusion, although we show that long-term survival is HIV-infected children treated with ART is relatively good, children are still being diagnosed late and starting treatment late, early mortality is high, and a significant proportion is lost to follow-up. While programs can use the good survival outcome to motivate caretaker to test and initiate ART early in children, more work is required to diagnose, initiate and keep children with HIV in care if we are to achieve the 95-95-95 goals by 2030.

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