Universal antiretroviral therapy (ART) for infants and young children living with HIV: assessing the effect of guideline changes on ART initiation characteristics and treatment outcomes in resource-limited settings

by

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Abstract

Background

Sub-Saharan Africa is home to >90% of all children living with HIV worldwide. Since 2008, there has been a shift in paediatric HIV treatment towards universal antiretroviral therapy (ART) allowing for immediate initiation of ART, regardless of clinical or immunologic status initially for infants, and subsequently for progressively older, and ultimately all children. Given the scale-up of early infant diagnosis (EID) and early initiation of ART for infants and young children who are especially vulnerable to rapid progression of HIV and mortality, access to paediatric antiretroviral therapy (ART) services has substantially improved across sub-Saharan Africa (SSA). However, with the changing guidelines and practices, the demographic and clinical characteristics of infants and young children infected in recent years may vary from those infected before the widespread uptake of prevention of mother-to-child transmission of HIV (PMTCT) services and universal ART. This study therefore sought to understand the impact of changing guidelines on key metrics of the paediatric HIV care continuum, including timeliness of ART initiation, mortality, program retention and viral load suppression in order to examine effectiveness of ART in infants and young children enrolled in routine ART programs.

Methods

Using data from the International epidemiologic Databases to Evaluate AIDS Collaboration (IeDEA), this thesis described the temporal trends in the ART initiation characteristics in a total of 1692 infants initiating ART <1 year of age and 32,220 young children initiating ART <5 years of age between 2006-2017 in South Africa and SSA respectively. The trends in outcomes including mortality, loss to follow-up (LTFU), viral suppression. Associated determinants were also examined.

Findings

The result chapters of this thesis are presented in the form of journal papers in different stages of publication. The first paper reports that disease severity characteristics among all children starting ART aged <5 years in sub-Saharan Africa improved over time. Mortality declined substantially, however, LTFU remained unchanged with one in five children continuing to be lost before two years on ART. There was substantial heterogeneity in outcomes across country income groups. The second paper presents data on infants with HIV starting ART ≤3 months of age in South Africa. Findings suggests a that growing proportion of infants started ART at younger ages and with less advanced HIV disease. Mortality was 10.6% (7.8%-14.4%) in 2006-2009 and decreases progressively to 4.6% (3.1%-6.7%) in 2013-2017 (p<0.001), with LTFU remaining unchanged across calendar periods (p=0.274). The third paper presents findings on the trends in viral suppression (viral load [VL] <400 copies/ml) and immunologic response up to 12 months on ART in infants who started treatment at <3 months of age. By 6 and 12 months on ART, 56% and 65% infants achieved virologic suppression and the median (IQR) CD4 percentages increased slightly to 30% (22-37) and 31% (25-39) respectively, from a median of 27% (18-38) at ART initiation. There was a trend towards poorer viral suppression levels among infants initiating early ART in recent calendar years, despite improvement in CD4% and lower VL at ART initiation. The final paper suggests that good long-term viral suppression (>70%) among infants in routine care is achievable. However, infants staring ART between 0-3 months vs those starting at 4-12 months of age had the lowest rate of viral suppression at all timepoints during a follow-up period of five years on ART.

Conclusions

Findings from this thesis suggest an increase in earlier ART initiation for infants and young children, with associated improvement in health status at ART initiation and declines in mortality following universal ART recommendations. However, substantial inequities existed across country income groups and a quarter of children on antiretroviral therapy across SSA continue to experience LTFU. In addition findings highlight suboptimal short and long-term viral suppression in infants acquiring HIV in the era of birth diagnosis and early infant ART. Targeted interventions are therefore urgently required to improve the outcomes of infants and young children living with HIV, especially among infants initiating ART before three months of age and children in low and lower-middle-income countries.

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Declarations

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The work included in this thesis is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely my own work or, in the case of multi-authored papers, constitutes work for which I was the lead author.

This thesis includes four manuscripts (two published, one submitted and one being prepared for submission) presented as result chapters. My contribution to each manuscript is outlined at the beginning of each results chapter. I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the following publications:

1. Iyun V, Technau KG, Vinikoor M, Yotebieng M, Vreeman R, Abuogi L, Desmonde S, Edmonds A, Amorissani-Folquet M, Davies MA, Variations in the characteristics and outcomes of children living with HIV following universal ART in sub-Saharan Africa (2006–17): a retrospective cohort study, The Lancet HIV,2021,ISSN 2352-3018, https:/doi.org/10.1016/S2352-3018(21)00004-7.

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3. Iyun V , Technau KG, Eley B, Rabie H, Boulle A, Fatti G , Tanser F, Wood R, Fairlie L, Mark C F, Davies M-A Virologic and immunologic responses to first-line antiretroviral therapy initiated during early infancy in South Africa.

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At the time of examination, two publications included were in their final published form. Per the university guidelines, the published chapters have been included verbatim in this thesis and in their original published format.

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List of abbreviations

ART	Antiretroviral therapy
AZT	Zidovudine
cART	Combination antiretroviral therapy
CI	Confidence interval
CLHIV	Children living with HIV
EIART	Early infant antiretroviral therapy
EID	Early Infant diagnosis
GEE	Generalized estimating equations
EFV	Efavirenz
HAZ	Height for age z-score
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IQR	Interquartile range
LBW	Resource-limited setting
LMIC	Low-and-middle-income country
LTFU	Loss to follow-up
MTCT	Mother-to-child transmission
NVP	Nevirapine
OR	Odds ratio
PCR	Polymerase chain reaction
POC	Point of care
PMTCT	Prevention of mother-to-child transmission of HIV
RLS	Resource-limited settings
RR	Risk ratio
SSA	Sub-Saharan Africa
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
VS	Virologic suppression
WHO	World Health Organization
WAZ	Weight-for-age z-score

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Chapter 1: Introduction

1.1 Introduction

1.1.1 HIV in children

Globally, an estimated 1.8 million children <15 years of age worldwide were living with HIV in 2018, approximately 90% in sub-Saharan Africa (SSA). While there has been substantial progress in reducing new pediatric HIV infections through successfully implemented prevention of mother-to-child transmission (PMTCT) programs, around half of approximately 150,000 new pediatric infections globally occurred in SSA. An estimated 100,000 pediatric HIV-related deaths occurred globally, nearly half in East and Southern Africa.[1]

The majority of new paediatric HIV infections occur among children aged 0-4 years, either during pregnancy, birth, or breastfeeding.[2] Due to the timing of infection and a rapidly developing physiology, specifically of the functional immune system, infants (<1 year old) have an exceptionally high risk of rapid HIV disease progression, HIV-related complications and consequent early death.[3] In the absence of antiretroviral therapy (ART), only 50% of infants living with HIV will survive up to two years of age,[4] with peak mortality occurring in the first 2-3 months of life.[5]

The introduction of combination ART for perinatally infected children living with HIV provided a paradigm shift that accounted for significant advancements in the management of paediatric HIV. More so, initiating ART immediately after diagnosis, and regardless of clinical or immunological criteria has substantially improved survival among children living with HIV.[3, 4] Yet, even after diagnosis and initiation of ART, infants and young children remain particularly vulnerable to poor outcomes. The highest post-ART attrition and mortality levels in children occur among children under two years of age.[5-7] In addition, HIV management in children is complex due to factors such as maternal antiretroviral drug exposure,[8] the timing of diagnosis and ART initiation, availability of age-appropriate regimen and dosage (especially for premature and low birth-weight infants),[9] and caregiver dependence.[10] Also, there are considerable challenges of providing comprehensive pediatric HIV care and monitoring of treatment outcomes in routine care resource-limited settings (RLS).[5]

1.1.2. Evolution of WHO treatment guidelines for children living with HIV

Over the past fifteen years, there have been significant advancements in the approach to paediatric HIV treatment, characterised by a shift away from age and CD4-related restrictions for ART initiation and towards universal diagnosis and treatment. A significant milestone was the introduction of combination ART in 2004, which changed the course of HIV in children and substantially improved survival. Furthermore, evidence continued to emerge demonstrating considerable survival benefit of immediate ART initiation compared to waiting for the WHO 2006 clinical and immunological treatment initiation criteria to be met.[11] The Children with HIV Early Antiretroviral Therapy (CHER) randomised clinical trial in South Africa reported a 75% and 76% reduction in mortality and HIV disease progression respectively, among infants living with HIV (median age at ART start 7.4 weeks) and receiving immediate ART compared to when ART was deferred until WHO 2006 criteria for ART initiation were met.[12, 13] Given this evidence, in 2008 the WHO recommended immediate ART for all infants with HIV under one year of age regardless of their clinical or immunological status.[13] Subsequent WHO guidelines have been progressively revised by increasing the age threshold for immediate initiation of ART. In 2010, it was recommended that infants and children below the age of two years start ART immediately after diagnosis irrespective of their clinical and immunological conditions. This age threshold was subsequently raised to five years in 2013,[12] and then removed altogether to allow treatment for all children with HIV in 2016. As part of efforts to prevent new perinatal transmission of HIV, the WHO, in 2013 recommended universal ART for all pregnant and breastfeeding women with HIV regardless of CD4 count either until the cessation of breastfeeding ("Option B") or lifelong ("Option B+").[14]

More recently, studies suggest that initiating ART as soon as possible after birth provides the possibility of functional HIV cure and has far-reaching benefits for improved survival, growth, and neurodevelopment.[3, 15-18] These reports build on evidence that supports ART initiation as early as in the first few days of life.[19, 20] A study in South Africa described a peak in early infant HIV-related mortality at three months of age.[21] Therefore, diagnosis at six or ten weeks of age with treatment initiation a few weeks later would be too late to prevent mortality in these infants. Given all available evidence, there is increased focus on diagnosing and initiating infants on treatment as early as possible, even earlier than children in the CHER trial.[19, 20]

Table 1.1. Changes in the World Health Organization's antiretroviral therapy initiation criteria for prevention and treatment of paediatric HIV from 2006-2016

Guideline	Age	2006	2008	2010	2013	2015	2016
ART initiation	<12 months	CD4 count <1500 or <25%	Treat all	Treat all	Treat all	Treat all	
	12-24 months	CD4 count <750 or <20%	CD4 count <750 or <20%				
	24-35 months		CD4 <350 or <15%	CD4 count <750 or <25%			
	36-59 months	CD4 count <350 or <15%	CD4count <350 cells/mm				
PMTCT	AZT starting T 28 weeks Single dose NVP			Option A (Maternal AZT+ infant NVP to end of breastfeeding) Option B (Maternal triple ART to end of breastfeeding)	Option B or B+ (lifelong maternal ART for all pregnant and breastfeeding women)		
EID			Virologic test: ≥6 weeks of age	Virologic test: 4-6 weeks of age	Virologic test 4-6 weeks of age	NAT at birth* high risk	NAT at birth for all
First line regimen	First NRTI	ABC, AZT or D4T		AZT or ABC or D4T	<10yearrs: ABC or AZT ≥10years: TDF or AZT		
	Second NRTI	3TC					
	Third ARV	NVP (EFV for children above 3years and >10kg)		<2 years: LPV/r (both NVP exposd and unexposed) 2-3 years: NVP >3years: EFV or NVP	<3years: LPV/r ≥3 years: EFV		

ABC: Abacavir, ART: Antiretroviral therapy, ARV: Antiretrovirals, AZT: Zidovudine, D4T: Stavudine, LPV/r: Lopinavir/ritonavir, EFV: Efavirenz, EID, Early infant diagnosis, NAT: Nucleic acid test, PMTCT: Prevention of mother-to-child transmission, NVP: Nevirapine, NRTI: Nucleotide reverse transcriptase inhibitor,

Early diagnosis is critical to the implementation of universal ART. Hence, efforts to scale-up early infant diagnosis (EID) programs across SSA are ongoing. Since 2010, the implementation of EID was supported by recommendations for using dried blood spot samples to increase reach and access. Furthermore, in 2016, the WHO expanded the guidelines for HIV PCR diagnostic testing at birth from testing for only high-risk HIV-exposed neonates to include all HIV-exposed neonates (universal birth testing) where feasible.[22] In SSA, an estimated half of all HIV-exposed infants receive an EID test within the first two months of life.[2] The most significant improvements in EID were observed in Eastern and Southern Africa, where 60% of HIV-exposed infants are tested by eight weeks of age.[2] Additionally, paediatric ART regimens recommended for HIV prevention and treatment have changed over time. Antiretroviral drug changes focused on improving palatability, bioavailability, ease of administration, storage, and transportation, especially in resource-limited settings (RLS).[23]

Taken together, these guideline changes have facilitated the achievement of crucial public health milestones, including the scale-up of access to (i) PMTCT programmes and subsequent decrease in MTCT, (ii) EID (iii) paediatric ART globally, and across SSA (Figure 1). In SSA, 52% of children now receive ART in 2019 compared to 17% in 2010. In addition, the removal of CD4 testing criteria and subsequent scale-up of EID is expected to reduce delays in ART initiation. Therefore it is likely that more children diagnosed with HIV will initiate ART when they are younger and healthier, and hence with a better likelihood of survival. In addition, simplifying ART initiation algorithms for children over one year of age was primarily aimed at providing programmatic benefits, especially to optimise care linkage and retention in care.

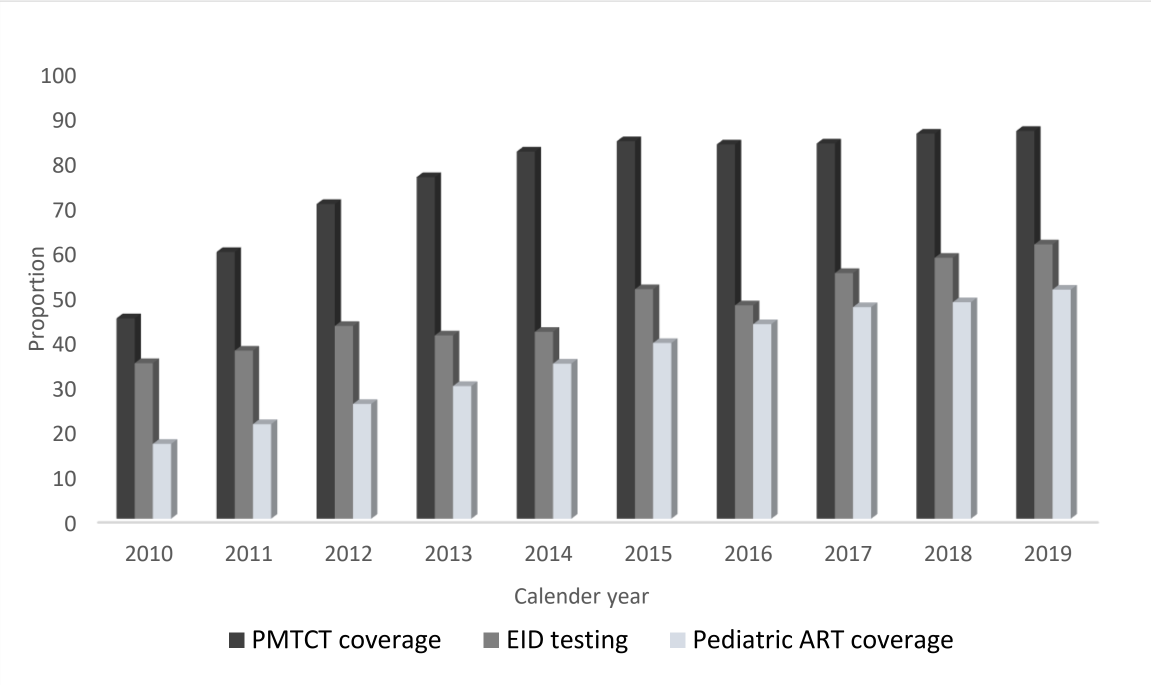

Figure 1-1 Trends in coverage of PMTCT, EID and paediatric ART in SSA between 2010-2019[1]

Despite the successes with universal ART guideline implementation and the consequent early diagnosis and treatment scale-up, the population-level impact of these changes over time in RLS remains unclear. Timely diagnosis and treatment of HIV infection remain a priority for reducing morbidity and mortality in children living with HIV. However, the increase in treatment coverage among children requiring therapy remains slow and uneven relative to adults. Also, there are a host of underlying factors such as malnutrition and other socioeconomic issues that may jeopardise real world ART effectiveness in these settings.[24]

Furthermore, the successful uptake of PMTCT and immediate ART could give rise to changes in the dynamics around HIV transmission, acquisition, and response to ART among infants and young children infected in recent years. Before the scale-up of effective PMTCT services, most new infections reflected a lack of widespread access to PMTCT services. However, more recently, MTCT occurs infrequently and may be suggestive of missed opportunities for diagnosis or prophylaxis during pregnancy and postnatally, especially in the context of widely available maternal and paediatric ART.

Furthermore, studies show an increased proportion of mothers with HIV-positive infants acquired HIV infection during pregnancy or early in the postpartum period. In 2019, 40% of vertical HIV transmissions were due to new maternal infections during pregnancy or breastfeeding, while an estimated 35% of mothers stopped use of their ART medication during pregnancy or breastfeeding.[1] Studies show an association between maternal acquisition of HIV during pregnancy and postnatally, and caregiver capacity to seek health care and adhere to medication.[25] Furthermore, poor medication adherence among caregivers could lead to treatment failure and rapid disease progression in their infants.[26] This ongoing shift in maternal characteristics among women with infants infected with HIV in the era of good access to universal lifelong ART,[27] means that infants and young children acquiring HIV in recent years may be very different socio-demographically and clinically to those infected before the option B+ era. In addition, there are increasing concerns around infant response to ART due to widespread in-utero exposure to ARVs or transmitted resistant virus.[28-30]

1.1.3 Paediatric HIV and treatment programs in sub-Saharan Africa

Epidemiology of paediatric HIV in SSA

Sub-Saharan Africa records the highest burden of paediatric infections worldwide, the majority (> 90%) due to perinatal transmission of HIV during pregnancy, at the time of delivery, or through breastfeeding.[31] Transmission in the postnatal period during breastfeeding is of particular concern. In 2015, more than half of new HIV infections in SSA occurred after six weeks of age, indicating breastfeeding transmission.[32] Approximately 50% of infants with HIV live in Nigeria, South Africa, India, Mozambique and Kenya.[33] Over time the number of new paediatric infections continues to decline. UNAIDS estimates describe a significant drop in MTCT from women living with HIV in Africa, declining from 22% (IQR:19.8-25.4%) in 2009 to 9% (IQR:8.0-10.0) in 2015.[32] This decrease reflects expanded access to PMTCT services across the region. Similarly access to ART for children who test positive has increased over time. These expansions in access to PMTCT and paediatric ART have been driven by progressively less-restrictive treatment initiation guidelines by WHO and national programmes. Nonetheless, only half of the children in need of treatment received ART therapy in 2019.[32]

Implications of universal ART on treatment programs in SSA

With an increasing number of children requiring treatment due to expanded ART eligibility comes an increasing demands on the already strained healthcare systems in RLS. Studies reveal that loss to follow-up may be increasing with the uptake of universal ART and subsequent increase in patient burden.[34, 35] Due to varying operational and financial capacity, there is a high variation in the implementation and scale-up of EID and early infant antiretroviral therapy (EIART) across SSA. For example, ART coverage among children 0-14 years of age during the period of 2010-2017 increased from 25% to 59% in East and Southern Africa compared to much lower coverage which increased from 8% to 26% in West and Central Africa.[1] Furthermore, over half (60%) of HIV-exposed infants in East and Southern Africa had access to HIV testing within their first eight weeks of life in 2015, while this proportion was much lower for West and Central Africa.[36] Paediatric HIV treatment programs in resource-limited settings continue to face persistent barriers at each step of the treatment cascade which negatively influence efforts to optimise improved health outcomes among children with HIV. These barriers include limited access to laboratory resources for EID and tests for treatment monitoring, limited availability of expertise for treating infants, particularly neonates, and the need to continual need for weight based adjustments of ART doses as the child grows.[37]

Considerations for early infant ART in resource-limited-settings

While there is a demonstrated improvement in survival when ART is initiated early in infancy, in routine care settings there is often a delay in infant diagnosis, leading to ART initiation after the onset of advanced HIV disease. In the CHER trial, 21.7% of children were excluded due to having advanced disease characteristics at enrolment. Also, in 2014 a study in Cape Town including 88 infants and 315 in Soweto with a median ART initiation age of 8.4 weeks, 62% already had advanced disease upon ART initiation.[38] In another study of 4945 infants under one year of age initiating ART between 2004 and 2012 at a median age of 6 months, 77% were reported to have WHO clinical disease stage three or four.[39] ART initiation early in life requires prompt diagnosis soon after birth and appropriate linkage to care. In many countries, linkage to care and ART initiation in infants and young children identified as infected remains suboptimal, with consequent poor outcomes compared to developed countries.[37, 40-42] Reports of high LTFU and mortality before ART initiation highlights programmatic difficulties in linkage to care in high burden settings.[6, 43] Nevertheless, a few recent studies have assessed very early infant diagnosis, providing evidence from routine programs supporting the feasibility of a first diagnostic test as early as the first day of life.[8, 19, 20, 44]

1.2 Rationale

With the shift in global guidelines and country practices towards the uptake of universal ART, including improved EID (including birth EID), and EIART, an increasing relative proportion of children are initiated on ART at much younger ages than was previously achievable. Clinical trials supporting these treatment recommendations are limited and existing studies mainly included older children (>2 years) and those healthier than usually managed in routine care settings.[4, 45, 46] Of note, infants included in the CHER trial started ART within three months of age (median age 7.4 weeks), were born at optimal gestational age and birth weight and did not have advanced HIV disease or co-morbidities at enrolment.[4]

Furthermore, the is a high variation in the progress in expanding these improved HIV care and treatment services across SSA. In addition, ART initiation among neonates poses additional challenges due to a more complex diagnostic and ART initiation process than older children.[3, 15, 47, 48] These necessary expertise and resources may not be accessible across all regions in SSA. Therefore, interpreting the intended goal of life-saving universal ART for paediatric HIV treatment requires special considerations for application in routine care programs in resource-constrained settings.

In RLS, a significant proportion of infants and young children continue to start ART with advanced disease.[5, 38, 39] In addition, characteristics such as prematurity, congenital infections, co-morbidities, low birth weight (LBW) and maternal social challenges may be increasingly frequent among infants acquiring HIV despite an effective PMTCT program. These characteristics may pose challenges to EIART implementation and hinder expected favourable outcomes. Also, given the advances in the effectiveness and scale of PMTCT since 2006 (notably the introduction of WHO Option B+ for PMTCT in many countries), vertically infected infants and children in recent years may differ substantially in characteristics from children acquiring HIV before the era of widespread Option B+. Hence well-conducted 'real-world' population-level studies assessing the impact of guideline changes over time are necessary to inform specific considerations for paediatric ART programs across SSA.

Similarly, the uptake and benefit of universal ART recommendation for young children older than one year is not well understood.[46, 49] It is unclear whether the postulated benefits of immediate ART in children 1-5 years are being achieved in routine care settings across SSA. While there is substantial evidence supporting the survival benefits of immediate ART initiation for infants aged 0-12 months, [3, 17, 18, 50, 51] there is less evidence on children initiating ART >1 year of age in the era of widespread ART. Furthermore these existing studies do not provide evidence on trends in outcomes across a time period of guideline changes.

Therefore, to better understand the influence of the World Health Organization's (WHO) universal ART guidelines changes over time, there is a need to investigate updated trends in the characteristics of children initiating ART and their clinical and programmatic outcomes. With the implementation of birth HIV PCR testing in some settings, infants start ART within the first days of life, much earlier than in the CHER trial. It is therefore unknown in research-controlled settings whether initiating ART closer to birth carries additional benefits for short and long-term outcomes. Additionally, programmatic difficulties in high burden settings remain and published data on 'real world' trends in characteristics and outcomes of infants and young children initiating ART are lacking. Existing studies either included a single cohort, were focused on older children above five years of age or did not include children starting ART in the Option B+ era. [27, 39, 43, 52-56] In addition, children on ART are living longer, and there is a need to examine the long-term outcomes of immediate ART initiated in infancy. To date, majority of published data reporting on long-term survival and virological outcomes beyond three years on ART are from resource-rich settings.[57-60]

1.3 Aim and objectives

1.3.1 Aim

The overall aim of this study was to examine the characteristics, outcomes and determinants of key treatment outcomes among infants and young children with HIV in the context of changing

WHO and national ART initiation guidelines towards recommending immediate ART for children and expanded effective PMTCT coverage, with a focus on infant outcomes.

1.3.2 Objectives

Objective 1: To examine the impact of changes in WHO paediatric HIV treatment guidelines and ART scale-up by describing the temporal changes in the characteristics of infants and young children starting ART in sub-Saharan Africa

Objective 2: To describe patterns and predictors of mortality and loss to follow-up after ART initiation over time in infants and young children starting ART in sub-Saharan Africa

Objective 3: To examine the trends and predictors of viral suppression on ART among infants starting ART at <3 months of age in South Africa

Objective 4: To describe long-term virological outcomes on ART in infants starting ART at <1 year of age and identify risk factors of virological non-suppression.

1.4 Data source

This research is a retrospective cohort study that analyses data collected across sub-Saharan Africa through the International epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration (https://www.iedea.org/). The IeDEA collaboration includes seven global regions, with 4 of these regions in SSA (Central, East, West and Southern).

IeDEA data are collated on-site by cohort investigators through routine clinical follow up of patients as part of standard monitoring of HIV. Anonymised data are then transferred to regional Data Centres using a data transfer protocol. IeDEA has existing mechanisms for combining data across IeDEA regions and conducting multi-regional analyses. The IeDEA Global Data Harmonization working group has existing processes for guiding data extraction and harmonisation from all IeDEA regions, including a data exchange standard with variable definitions and standardised codes. In addition, the IeDEA Global Paediatric Working Group identified infant and young child ART outcomes as a research priority and was supportive of the analysis. Each of the IeDEA regional collaborations combines and analyses data from several HIV cohorts to address HIV/AIDS research questions that cannot be addressed within a single cohort. For example, IeDEA-Southern Africa (IeDEA-SA) includes data collected from 15 ART programmes in 6 Southern African countries (Lesotho, Malawi, Mozambique, South Africa, Zambia and Zimbabwe), and the combined database contains patient-level data on >50,000 children that have initiated ART. The other IeDEA regions in Africa include data on >25,000 children from 16 countries.

This research project utilised data of >30,000 children with HIV from the IeDEA African regions in Central, East, West and Southern Africa to address Objectives 1 and 2 and routine IeDEA data from >1500 infants living with HIV in South Africa to address Objectives 3 and 4. Clinical sites included in the study represent various settings ranging from primary care clinics to secondary hospitals and tertiary referral centres.

1.4.1 Ethics

There is existing ethical approval from the University of Cape Town Faculty of Health Sciences Research Ethics Committee (UCT-HREC) for analyses conducted on IeDEA and IeDEA-SA data. Each cohort has institutional ethical approval to contribute data to IeDEA analyses. Additional approval specific to this research for the PhD degree was obtained by the UCT HREC (Ref number 087/2019).

1.5 Thesis overview and structure

This thesis consists of seven chapters including an introduction chapter , a literature review, four result chapters and a discussion chapter.

Following this introductory chapter, Chapter 2 details a literature review that focuses on the existing evidence of outcomes of infants and young children on ART. This section provides a background to this thesis on each key aspect of focus: characteristics at ART start, mortality, retention, and viral suppression. Chapter 3-6 includes four results chapters presented as papers which have been published, submitted and been prepared for submission.

Chapter 3 addresses the first and second objectives of the thesis by assessing the effect of the expansion of ART eligibility criteria on the characteristics and outcomes of young children starting ART within five years of age in SSA. This chapter examined the trends in the uptake of early infant ART in the region (by assessing the proportion of infants starting ART <3 months of age), characteristics of children starting ART and outcomes including mortality and LTFU. These analyses address the gap in the literature by describing patterns in characteristic and outcomes over 12 years and disaggregating findings by age. Findings from this chapter provide new data on variations in the improvement in outcomes across country income groups which is relevant to the sustainable development goals (SDG), in particular goal 10 which aims to reduce inequality within and among countries. Using survival analysis, determinants of mortality were assessed with an additional demonstration of the potential effect of mortality under-ascertainment on findings.

Chapter 4 builds on findings from Chapter 3 also covering objectives 1 and 2 but with a specific focus on EID and treatment. There is a high uptake of EID, including birth PCR testing and EIART, and a substantial number of infants starting therapy in South Africa, as observed from the earlier chapter. Therefore this chapter extends existing evidence on the benefits of early ART to include trends in characteristics at ART start, mortality and LTFU in a large cohort of early-treated infants over a period of twelve years. Findings from this chapter suggest that improved survival of children over time is mediated by earlier ART initiation and improved disease severity characteristics at treatment initiation.

Chapter 5 addresses the third objective of this thesis by describing how the rates of short-term viral suppression among early treated infants have changed over time and by examining the predictors of non-suppression. Virologic outcomes among infants in SSA have been assessed, and evidence shows that achieving viral suppression among infants is challenging. However, few studies show how expansion in PMTCT and ART over time may be related to trends and variations in viral suppression. Given the current era of widespread ART, fewer new paediatric infections and increased relative proportion of high-risk infants among those acquiring HIV, paediatric HIV care is moving towards a more tailored approach for effective interventions. This approach enables the identification of infants who need closer monitoring especially shortly after ART initiation. Conclusions from this chapter suggest that suboptimal viral suppression among infants has worsened in more recent cohorts. It also argues that other factors besides early diagnosis and treatment, such as maternal characteristics, need to be considered to optimize treatment response.

Chapter 6 addresses the fourth objective of this thesis by exploring the long-term outcomes of early infant ART. It specifically focuses on long-term viral suppression among infants starting ART during infancy (<1 year of age), describing viral suppression for up to five years on ART. This analyses found good viral suppression at five years on ART, however infants starting ART before three months of age were less likely to be suppressed at all timepoints on ART. Findings highlight the need for focus on challenges related to neonatal ART in RLS, especially in the era of EID and EIART.

Chapter 7 presents a discussion of the findings of this thesis. This chapter synthesises and contextualizes the results of this project and discusses the public health significance and implications of the results of this thesis. This chapter also offers recommendations for further research focus and potential interventions based on the specific evidence obtained in this work.

1.6 Public health significance

This thesis provides insights on ART treatment outcomes among infants and young children living with HIV in routine care resource-limited settings in the context of improved PMTCT coverage, WHO ART eligibility guideline criteria changes and changing practices towards earlier infant diagnosis of HIV, including diagnosis at birth. Findings will potentially inform the implementation of paediatric ART guidelines by identifying predictors for poor outcomes and feasible interventions and models of care to better optimise HIV management in infants and young children in the current context of rapid ART-scale up. South Africa has recently rolled out birth HIV testing, allowing infants to start on ART in the first days to weeks of life. Therefore, by assessing EIART programs in this setting, findings from this thesis could potentially provide vital evidence to inform optimal EIART implementation in other settings across SSA. This analysis benefited from existing collaboration across different sites and settings considering the relatively few patients at participating IeDEA sites, and that stable infants may be transferred to lower levels of care which limits comprehensive evaluation of their outcomes unless there is collaboration between care sites.

Given that this thesis utilised large routine-care HIV cohort databases within the IeDEA Global Consortium, findings would likely be generalisable to the paediatric HIV population in SSA. The IeDEA Global Consortium has in the past contributed to informing global paediatric HIV estimates and guideline development. Therefore, results from this study are strategically placed to inform future development or improvement of treatment guidelines for infants and young children living with HIV. Findings also provide insights into interventions tailored specifically to the emerging needs of those more recently infected.

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Chapter 2: Literature review and research gaps

2.1 Overview

This literature review aimed to provide a context for this thesis by presenting a summary of existing knowledge focused on the health outcomes of early-treated infants with HIV. For the purpose of this review, ART will be defined as a regimen of antiretroviral drugs from at least two different drug classes. Infant will be defined as age <1 year according to WHO classification. The terms 'universal ART', 'immediate ART' and 'early ART' will be used interchangeably as documented in the literature.

This review synthesises relevant knowledge related to immediate ART outcomes among infants, summarised into four questions:

1. What are the implications of universal ART for infants living with HIV in resource-limited settings?
2. How have the characteristics of infants at ART initiation changed over time?
3. What are the trends in short and long-term outcomes of early infant ART?
4. What are the determinants of mortality and virological non-suppression among infants initiating early ART?

Each of these aspects is discussed as an important factor in relation to the scale-up of universal ART diagnostic and treatment practices for infants and young children. This review is organized according to the objectives of this thesis and focuses on the key constructs of interest. Findings from key studies from sub-Saharan African cohorts that present findings on ART initiation characteristics, mortality, retention and virologic outcomes will be reviewed. To provide an overview of findings, tables are used to summarise the results of some key studies focused on infants starting ART at <1 year of age in SSA. However, I will also include selected studies from developed countries that present findings critical to the objectives of this study and for important contextual comparisons. This literature review chapter is not intended to provide a systematic review of all available studies, but rather to present important findings from the literature to provide a better understanding of existing evidence on early infant ART outcomes in the era of widespread ART for prevention and treatment.

A search in PubMed was conducted for literature on early infant ART and outcomes from studies in SSA. The search was restricted to articles published between 2004 and 2020 and used the following terms: ((((HIV) AND (Infants OR children)) OR (early infant antiretroviral therapy OR universal antiretroviral therapy OR immediate antiretroviral therapy) AND (mortality OR outcomes)) OR (virologic suppression OR viral suppression OR virologic outcomes)) AND (loss to follow-up OR retention OR LTFU). Additionally, the "snowball" method was used to identify other relevant literature from the reference list of identified articles.

2.2 What are the implications of universal ART for infants living with HIV in resource limited settings?

Universal ART affords for infants and young children to be started on ART immediately after diagnosis, prior to the onset of advanced HIV disease. Prior to 2008, children starting treatment needed to fulfil a criteria of having WHO disease stage three or four or CD4 percentage < 20% (12-26 months of age), or a CD4 percentage of <25% for infants under 12 months of age. The CHER trial catalysed a paradigm shift in the way infants with HIV are diagnosed and treated. In addition, other observational studies suggested substantial survival and growth benefits of ART started irrespective of infants' clinical or immunological status.[1-3] Therefore, current WHO guidelines recommend immediate initiation of lifelong ART in all children, an expansion of the initial recommendation limited to infants under the age of one in 2008.[4] In addition to survival benefits, anticipated programmatic benefits of universal ART include the potential to increase treatment coverage and improve patient retention.[2, 5-8]

Universal ART for infants, also referred to in this thesis as early infant ART, is crucial due to certain biological factors that influence the natural course of HIV disease. One of the factors contributing to the recommendation of immediate ART in infants is the characteristically weaker prognostic significance of the CD4 criteria and rapid disease progression leading to early death in the first two years of life.[9] Similarly, a distinctive feature of viral load in infants is a high pre-treatment viral load and slow decline post-ART initiation, making viral load a poor marker of ART effectiveness during early infancy.[10] Furthermore, infants living in RLS face additional challenges in starting ART including limited access to laboratory testing including CD4 tests, limited availability of antiretrovirals and limited clinical expertise in managing infants with HIV. Therefore, starting all infants and young children on immediate ART allowed for increased access to paediatric ART in these settings, given that ART initiation was no longer dependent on a CD4 test result.[11]

Although early diagnosis and initiation of ART for infants may be beneficial for mid to long-term survival,[6] lifelong treatment presents certain programmatic challenges with implementation especially in high-burden resource limited settings.[12-16] Some of these emerging challenges include development of drug resistance,[17] increased rate of antiretroviral drug toxicities, adverse events particularly in neonates, and increased burden and cost to the health care system.[18] Also, with the intense focus on achieving the 90-90-90 targets in adults and the decreasing number of infants with HIV, there is a risk that infants living with HIV may increasingly become less of a priority group in the context of busier health services attempting to provide access and retain growing numbers of patients on ART. This is evident from the limited published data regarding universal ART outcomes in infants and young children. WHO recommendations were primarily based on a public health approach and programmatic considerations especially for RLS with difficulties such as poor clinical monitoring for CD4 and viral load and high rates of LTFU. However, with more infants getting initiated on ART, evidence shows that LTFU may be increasing over time.[19-21] Other programmatic challenges include lack of adequate expertise and resources for treating neonatal HIV, suboptimal clinical monitoring, and patient tracking.[22-25]

Furthermore, there are maternal-related challenges to be considered given the caregiver dependence among infants living with HIV. The progressive expansion of ART initiation age criteria and PMTCT coverage could impact maternal characteristics over time. It is expected that the demographic characteristics of women experiencing perinatal transmission of HIV is evolving. An increased risk of perinatal transmission of HIV has been associated with maternal ART initiated late in pregnancy with very low CD4 cell count (<350 cells/µl) and high viral load compared to women who were diagnosed and started on ART prior to their recent pregnancy.[26] Another study showed that maternal acquisition of HIV during pregnancy contributes substantially to new paediatric infections. [27] One hypothesis to consider is that new paediatric infections are likely occurring among children born to mothers who did not engage successfully or were not retained despite good coverage of effective PMTCT services.[28] In RLS, these clinical factors are commonly linked to pre-existing socioeconomic and psychosocial issues. Therefore poor medication adherence and health service engagement which extends to infant care, are likely to be increasingly prevalent among infants with HIV over time.

There are also infant factors associated with a higher risk of paediatric HIV infection including congenital infections and comorbidities.[29, 30] These characteristics may become relatively more common among infected infants acquiring HIV because PMTCT gaps are now much less common after 2013. [30, 31] In the absence of ART, intrapartum infections account for most early infant HIV acquisition events. However, in the context of effective PMTCT, in-utero infections out-number intrapartum infections by up to three to one.[32] Thus, infants with HIV diagnosed and treated in the pre-universal ART and Option B+ era are likely to have different characteristics to the infants acquiring HIV after 2013. Furthermore, in-utero infected infants have been shown to have poorer survival compared to those infected postnatally.[33, 34] High mortality of approximately 12% by one year on ART was demonstrated among infants with HIV identified at birth.[35] Therefore, with an increasing relative proportion of infants acquiring HIV in-utero over time, there is a need to better understand the differences in infant characteristics among newly infected infants compared to historic cohorts. It is also essential to describe how these changing characteristics may impact outcomes and care requirements in resource-limited settings.

2.2.1 Early infant diagnosis and antiretroviral therapy

Since the introduction of universal ART by the WHO, countries in SSA have made efforts to implement the guidelines recommending testing infants as soon as possible and provide better access to paediatric ART. However, country uptake of universal test and treat guidelines for infants have varied especially with regards to early diagnosis for infants under two months of age and early infant ART. Nevertheless, countries like South Africa have made giant strides in implementing EID and EIART. Being able to identify infants very early and initiate them on ART has proven benefits which span beyond preventing morbidity and mortality.[8, 36] Very early ART may affect immune development in the lon-term, growth recovery and virologic control. [29, 32, 37, 38] Furthermore, a few studies have demonstrated the possibility of sustained viral suppression [38], and possible functional HIV cure [39] after reports of the "Mississippi baby" who sustained viral suppression for 27 months after initiating ART within 30 hours of birth.[40] A similar finding was also reported in a nine year-old child in South Africa who remained supressed virologically for 8.5 years without antiretroviral drugs after initiating ART in infancy.[41]

To effectively implement universal ART for infants there is a need for prompt and improved EID practices.[42] Based on increasing evidence on the benefits of ART started very early in life, there is more emphasis on starting ART in the first few days of life as opposed to starting between four to six weeks of age according to the results from the CHER trial.[43] Studies show that the peak mortality period for infants without ART is 2-3 months of age, therefore the timing for diagnosis of all exposed infants by two months of age is too late.[44] Additional evidence from the children screened for enrolment in the CHER trial sites suggest rapid disease progression during infancy with 62% of infants having advanced HIV disease at the time of ART initiation (12 weeks of age).[45] Therefore starting ART as soon as possible after birth could have additional survival benefit. Earlier diagnosis provides many potential gains in addition to the direct benefit of starting ART earlier. Earlier diagnosis may help close the gap between diagnosis and linkage to care where substantial LTFU occurs due to the waiting period for children to attain CD4 or immunologic criteria. Studies show a high occurrence of LTFU prior to initiation of ART during early infancy.[46, 47] This pre-ART LTFU has been attributed to unascertained mortality due to the characteristic high early mortality among infants. Specific EID efforts include the introduction of point of care testing (POC) and an additional birth PCR test which allows for detection of in-utero infections and earlier linkage to care and improved retention in care.[32, 37]

2.2.2 Programmatic and diagnostic challenges of early infant diagnosis and antiretroviral therapy

There are many barriers to the expansion of EID programs in RLS, particularly in rural settings with limited access to laboratory facilities. Challenges include inadequate human resources and expertise for neonatal HIV treatment including preterm and small for gestational age infants, difficulties with transportation and communication between the centralised laboratory and the primary care clinics, delays in sample-result turnaround times and limited affordable ARV formulations.[45, 48, 49] Furthermore, there are only few licensed drugs with suitable dosage for infants, particularly for neonates including preterm infants. Also, the dosage requires constant change in relation to the weight of the infant. Logistically, after diagnosis children usually have to be referred to a different site for ART initiation which causes further delays. Data from Zambia in 2014 showed that the median time between sample collection and communication of results to the caregiver was 85 days.[50] Problems cited were delays in result turnaround from the central laboratory to the health facility and then to the caregiver.

Earlier diagnosis and treatment initiation require additional financial resources. Costs related to universal ART implementation include the need for reliable viral testing for EID programmes. Effective virologic monitoring to assess responses such as treatment failure and virologic resistance is crucial especially in infants with prior PMTCT exposure.[51, 52] Studies from Malawi and South Africa revealed that early diagnosis of HIV did not necessarily translate into early treatment initiation.[46, 47] The rate of ART initiation was slow, and mortality remained high. These findings emphasize the complicated nature of clinical care of infants and the difficulties of implementing WHO guidelines in real-world settings. Innovative and targeted interventions are needed to ensure that infants in routine care resource-limited settings experience the benefit of universal ART.

2.3 How have the characteristics of infants at ART initiation changed over time?

ART initiation characteristics of children such as age, CD4 count and percentage, WHO clinical disease stage and weight-for-age z-score (WAZ) are important measures of early ART initiation. Assessing these characteristics upon diagnosis and program enrolment serve as a measure of the extent to which early HIV diagnosis before disease progression is being achieved. In addition, several studies show the effect of characteristics such as age and disease stage on survival and related outcomes.[24, 38, 49, 53, 54] This section focuses on the progress in early ART initiation and will therefore report on studies assessing trends in infant characteristics upon treatment initiation.

2.3.1 Age

Temporal trends in the age of children starting ART provides a measure of advancement towards earlier ART initiation and how well EID is being implemented. It is expected that as the coverage of EID and EIART programs increase, there would be an increase in the relative proportion of infants with HIV who are diagnosed at increasingly younger ages.[55] In Zambia, a study carried out between 2006 and 2016 reported that the average time from diagnosis to ART initiation decreased from 220 days in 2006 to 9 days in 2016.[56] Another study including 86 infants initiating ART in South Africa showed that the median age at ART start decreased from nine days between 2013-2014 in the era before universal HIV birth testing to two days after 2014 when universal HIV birth testing and point of care testing were introduced.[57] Nevertheless, this study was focused on infants tested at birth in a maternity facility, therefore the findings may not be generalizable across South Africa.

Despite existing challenges to EID and EIART scale up in SSA, some settings in SSA such as South Africa and Rwanda have achieved substantial success in the coverage of EID including HIV birth testing and subsequent early ART.[58-60] Furthermore, previous data from Kenya, Mozambique, Rwanda and Tanzania showed that the proportion of children starting ART before two years of age increased from 12% in 2005 to 33% in 2011.[61] Another large study including 30,000 children initiating ART showed an increase in the relative numbers of children starting ART under one year of age from 12 to 19%.[55] Yet, there remain limited studies on recent temporal trends in the age at ART initiation of infants with HIV at <1 year of age (Table 2). A few studies suggest a trend towards decreasing median age of infants initiating ART over time.[55, 62, 63] The only multi-cohort study of infants initiating ART in routine care before one year of age in Southern Africa showed a decrease in the median age of ART start from 6.1 months between 2004-2009 to 5.4 months between 2010-2012.[48] However, it is important to note that this study was conducted before the introduction of EID in South Africa.

In contrast, settings with very successful PMTCT such as high income and developed countries report an rise in median age of children with HIV starting ART due to a near eradication of new paediatric HIV infections in these settings.[64] An understanding of the age at which infants are started on ART and how this has changed over time, will offer a better understanding of the influence of universal ART on children enrolled in routine care settings.

2.3.2 HIV disease severity

Advanced HIV disease is defined by the WHO as having WHO stage three or four or a CD4 cell count <200 cells/ µl in children older than five years of age. All children under the age of five years were considered to have advanced disease in the WHO Guidelines for managing advanced HIV disease and rapid initiation of ART for several reasons.[65] First, at the time of guideline development, most children younger than five years were shown to already have severe immunosuppression upon presentation for care. Second, younger children have a higher risk of rapid disease progression and mortality regardless of clinical and immune status. Third, there was a need to decrease the additional difficulty of using age-related CD4 cell count definitions for advanced immunosuppression in children younger than five in routine care settings.[65] Other markers of severe HIV disease such as being underweight (WAZ <-2) have been strongly linked to mortality among infants with HIV and young children.[16, 45, 66, 67] With EID and EIART, an increasing proportion of infants and young children should start ART prior to onset of advanced HIV disease. Among infants in particular, delayed ART initiation is a main concern due to the substantial benefit for reducing rapid disease progression, morbidity, and mortality. Earlier studies including children initiating ART before 2010 showed that around 50-60% started ART with WHO stage 3 or 4.[55, 62] More recent studies show that this scenario is changing with a range of 16-30% of children starting ART with advanced disease and the prevalence of underweight is suggested to be decreasing. [48, 55, 62 35, 46, 62, 68] However, some recent studies show that approximately half of infants with HIV in SSA still start ART with advanced HIV disease. [48, 68]

Table 2.1. Characteristics at ART initiation among children initiating ART before one year age in sub-Saharan Africa

Author, year	Country	Study period	Number of children	Median age at ART start (months)	Median CD4	% advanced disease (CD4 <25% stage 3 or 4	Median WAZ	Median VL
Prendergast, 2008	South Africa	2003-2005	40	1.3 (0.2-12.8)	30 (17-43)	NR	NR	952000 (0.2-3.7 x 10^6
Violari, 2012	South Africa	2005-2007	252	7.4 (6.6-8.9)	35.1 (29.1-40.8)	NR	-0.8 (-1.5, 0.0)	NR
Asbjornsdottir, 2016	Kenya	2004-2007	121	3.9 (3.5-5.0)	21 (16-29)	NR	−2.4 (−3.8, −1.0)	6.6 (6.1, 7.0)
Purchase, 2012	South Africa	2005-2008	94	8.6 (2.1-11.9)	15.4 (0.1–43.4)	NR	-2.7 +/-1.97	6.2 (1.4-7.9)
Palumbo, 2010	South Africa	2006-2009	NVP group 60	0.6 (0.5-0.9)	19.2 (12.0-31.4		-1.2 (-3.2, 0.8)	5.9 (5.1-5.9)
			Lop/r group 63	0.6 (0.5-0.8)	21.2 (14.0-30.6)	NR	-0.9 (-2.6, 0.5)	5.9 (5.2-5.9)
Davies, 2013	South Africa	2005-2010	30,300	6.1	17.9			
Inness, 2014	South Africa	2007-2010	403	8.4 (7.2-9.7)	29 (23-37)	62%	NR	
Wamalwa, 2012	Kenya	2007-2009	80	3.7 (2.9-4.0)	18 (14–24)			6.59 (5.98–7.21)
Tejiokem, 2015	Cameroon	2007-2011	192	4.1				
Porter, 2015	South Africa, Zimbabwe, Malawi, Zambia	2004-2012	4945	5.9 (3.7-8.7)	18.5 (12-26)	71%	-2.5 (-3.9, -1.2)	5.99 5.41-6.45
Tukei, 2013	Uganda	2009-2012	91	6.2 (4.0-9.0)	20 (15-29	55.6	−2.2 (-3.89, -1)	18.2% < 100,000
Ndongo, 2018	Cameroon	2008-2013	190	4.0 (3.0–5.6)	23.0 (15.0–31.8)	NR	0.2 (0.0–0.4)	6.5 (5.4–7.0)

VL: Viral load; WAZ: Weight-for -age z-score; NR: Not recorded; NVP: Nevirapine; Lop/r: Ritonavir boosted Lopinavir

2.4 What are the trends in short and long-term outcomes of early-treated infants?

2.4.1 Mortality

Mortality is the most important and most commonly reported ART outcome. Sources of mortality documentation in paediatric HIV care include national vital registries, hospital patient documentation and, less frequently, findings from community tracing efforts. Evidence from observational data from routine programs in RLS suggest variable mortality rates among infants with HIV initiating ART.[69] A systematic review conducted including 30,000 with HIV and under ten years of age indicated that 5-29% of children initiating ART were either dead or LTFU after one year on treatment.[70] A cumulative incidence of mortality between 4-7% by one year on ART was observed among children with HIV starting ART <15 years of age in other African countries. [16, 48, 67, 71, 72] Reports of mortality at two years on ART from routine programs in RLS ranged from 4 to 29%. [46, 69] A more recent systematic review reported a cumulative proportion of mortality of 3, 5, 6 and 7% by 3, 6, 12 and 24 months on ART respectively.[73]

Very few observational studies present mortality trends over time for children starting ART during infancy. A study of 4945 infants with HIV in Southern Africa initiating ART before one year of age (median 5.9 months) from 2004-2012 had a six and twelve month cumulative probability of mortality of 10% and 13% respectively.[48] This study also noted significantly lower mortality after 2010, when WHO implemented universal ART for all children <2 years of age.[48] However, this study only included a relatively small number of infants <3 months at ART start with limited follow-up beyond 2010. In addition, most infants who started ART after 2010 had severe HIV disease and were >3 months of age at ART start, which is well beyond the median age of ART initiation (7 weeks) in the CHER study. Another study from a single facility in Johannesburg revealed high mortality of 12% after one year on ART among infants identified at birth.[57] Importantly, this study noted high mortality before the start of treatment as documented in previous studies.[46, 47, 57, 74]

The first year on ART is particularly critical as a substantial proportion of infants die during this period, especially in the first three months after treatment initiation.[44, 75] High early mortality in the first few months post ART initiation among infants and young children has been demonstrated by several cohort studies across Africa and is largely associated with high levels of immunosuppression upon ART initiation. [44, 47, 49, 54, 76] This trend in high early peak mortality within the first 2-3 months on ART has been suggested to persist despite improvement in access to ART.[57, 73]

Existing evidence reflects a paucity in the knowledge of population-level outcomes of infants who start ART without severe disease, particularly after implementation of Option B+. Also, there have been no studies assessing temporal trends in mortality among early-treated infants starting ART before three months of age in SSA. Similarly, data on long-term survival and viral suppression are mostly from high income countries or include older children (>5 years of age at ART start). [77-81]

2.4.2 Retention in care

The proposed benefits of universal ART would only be realised if children are retained in care with access to close clinical monitoring. However, the context of program engagement in children is more complex compared to adults. Hence, LTFU among infants in routine care paediatric HIV programs in resource-constrained settings remains a recognised challenge.[70] Additionally, several context and health system factors contribute to high LTFU among infants in RLS. Infants and young children depend on their caregivers for engagement with the health system; therefore, their health outcomes are associated with those of their mothers or caregivers.[82] There are several factors that may impact retention of women living HIV and by extension their infected infants. Studies have demonstrated that postnatal retention in care of mothers, particularly younger mothers (<25 years old) is poor.[83, 84] This may suggest corresponding difficulties with retention of infants during this period in a mother's life which is often challenging, involving the added responsibility of a new child and coming to terms with the diagnosis of HIV in her infant. Also, the location of paediatric ART services, treatment sites (hospital vs. primary health care) and a lack of service integration of maternal and child services in many RLS have been found to contribute significantly to LTFU.[66, 70, 82, 85] This fragmented nature of EID and infant ART increases the chance of a child being lost by the addition of extra steps in the care cascade. Likewise, the impact of Option B+ on retention among pregnant and postpartum women living with HIV remains inconclusive. A study in Malawi reported that women experiencing same-day ART initiation after diagnosis in the era of Option B+ were twice as likely be LTFU after ART initiation relative to women who started ART later.[21] In contrast, some studies suggest better retention with immediate ART initiation.[86, 87]

Furthermore, while universal ART for children could in theory contribute to better retention, it has been associated with higher LTFU than when ART was deferred until disease severity criteria were met. A number of cohorts of African and Asian children had higher levels of LTFU among children starting ART in later years compared with ART initiation in earlier years.[82, 88, 89] In Southern Africa, despite improvements in program outcomes observed after 2010 among infants with HIV starting ART <1 year of age, LTFU remained high (19%).[48] This may be because healthier children are now starting ART, therefore caregivers may lack motivation and may be more likely to drop out from ART programmes during follow-up. Studies also suggest that rapid decentralisation of services contributed to an increased burden on the already strained health system and consequent poor documentation of patient transfers, which may artificially inflate LTFU. [20, 63, 85] However, findings of poorer retention on ART in the universal or immediate treatment era may be subject to bias because patients that may have been LTFU prior to ART initiation may now be LTFU after ART start in the era of universal ART, thereby shifting "pre-ART LTFU" to "on ART LTFU".

LTFU is higher among infants and young children compared to older children >2 years of age. A study from Rwanda reported high patient retention in children <15 years of age with a 1% cumulative incidence of LTFU by one year on ART, nevertheless younger infants remained the most vulnerable to being lost.[90] There are several possible explanations for higher LTFU in infants. First, there may be a high level of misclassification of deaths among infants. Given that infants are at higher risk of death than older children, especially if they start ART with advanced clinical disease, many deaths may go unrecorded and are misclassified as LTFU. LTFU among infants has been shown to be highest in the first few months after ART initiation. This period shortly after ART start coincides with the highest risk of death, strongly suggesting that some of those LTFU may be children who actually died prior to their scheduled visit. [20, 48, 91] A study that included children 0-14 years of age initiating ART in four sub-Saharan countries; Kenya, Uganda and Malawi reported high LTFU during the first three months after ART initiation (incidence rate ratio (IRR) = 2.49 for 0–3 months and 1.51 for 4–6 months, compared to 7–24 months following ART initiation.[92] Another report of children (age 0-14 years) initiating ART in Ethiopia described a risk of LTFU of 7.7%, 11.8% and 16.6% at 6, 12 and 24 months of follow up, respectively.[91] Similarly, evidence from four treatment programs in Africa reported 16% and 22% LTFU at six and twelve months on ART with the highest rates observed in the first six months and declining through 12 months on ART.[61] Some studies that traced patients LTFU suggest mortality may be high in this group.[22, 94] Secondly, reliance on caregivers who may themselves have challenges with being retained in care, especially mothers of infants acquiring HIV despite high coverage of effective PMTCT, may negative impact retention. A study in Malawi showed 17% of women with HIV initiating ART under Option

B+ were LTFU by six months postpartum, and most losses occurred within the first three months.[21]

2.4.3 Mortality under ascertainment and interpreting mortality estimates in resource limited settings

There remains concerns about accurately comparing mortality across different settings in RLS due to varying proportions of undocumented deaths considered as LTFU and varying resource capacity across paediatric HIV programs.[89] There is a paucity of recently published studies that assess mortality among all HIV-positive infants who enrolled in care, not just those that started ART. The few existing studies include very few infants and mostly assess only pre-ART mortality.[46, 47] Interpreting LTFU depends largely on key factors including definition of time away from the service, the length of follow up, adherence support system and tracking practices at the facilities. Furthermore, the definition of LTFU in children living with HIV varies considerably among studies and rates differ widely across settings in RLS. The gap in HIV care considered to comprise LTFU in most studies ranges from 1-6 months without contact with the health care service prior to database or study closure.[70, 89, 93] In addition, variability of referral practices and poor documentation of patients transferred out, limits comparison across programs and regions.

In summary, LTFU in many settings remains largely overestimated due to under ascertainment of mortality and unrecorded transfers to another facility.[22] The influence of universal ART on retention of children over time, especially among asymptomatic infants in the Option B+ era remains unclear.

2.4.4 Viral suppression

HIV viral load (VL) remains the primary measure of HIV treatment success and children living with HIV are a priority group for routine VL monitoring according to WHO 2016 guidelines.[95] With the advent of very early infant ART, research has demonstrated the possibility of sustained viral suppression, viral remission, and possible functional HIV cure.[39, 40, 96] Starting treatment in the first days or weeks of life should result in improved virologic outcomes compared to starting at older ages, however, infants may have elevated viral loads at the start of treatment with slow suppression on treatment compared to older children.[10] The level of VL monitoring remains suboptimal in many resource-poor settings mostly due to inadequate laboratory facilities and trained staff. [97] Until recently, data has been limited on viral suppression levels in children in RLS who are routinely monitored compared to a more focused approach when children are only tested if they show signs of clinical treatment failure or immunosuppression.

Overall, the proportion of children who achieved viral suppression as reported in studies across SSA varies greatly (Table 2). Also, the threshold used in assessing viral suppression is highly varied across studies. Infants (median age 3.9 months) have been shown to achieve viral suppression at a much slower rate compared to older children (median age 4.8 years).[10] Observational studies in routine care settings have also shown considerably higher rates of virologic failure in infants compared to older children.[98, 99] Among infants, early ART is expected to improve viral suppression compared to starting in later infancy as viral replication is limited from earlier on. However, there are conflicting results on whether infants starting ART at very young ages have better suppression than those starting at slightly older ages. A recent study including three cohorts of infants with HIV starting ART in Johannesburg found no difference in initial virologic suppression among infants who started treatment before six months of age and those starting between six and twenty-four months of age. Only 31%, 40% and 26% of infants starting ART before <6 months of age in the three cohorts respectively were suppressed below 50 copies/ml by 6 months on ART.[100] Furthermore, some studies from high income countries have described improved short and long-term viral suppression in children started on ART <3–6 months of age compared to children started after 6 months of age,[78, 101, 102] while others have shown no differences in the rates short-term virological suppression.[102] Findings of infants starting ART in the first months of life also revealed varying levels of viral suppression.[40, 103] In addition, studies conducted in the era of birth HIV testing revealed no consistent difference in virologic response to early ART among infants starting ART earlier vs later. For example, there was no difference in virologic response to early ART by 12 months on ART in those starting ART <48 hours after birth and those starting between 48 hours to 7 days (73 vs. 66%, p=0.79). Among 30 infants initiating ART between 0-15 days, about half suppressed virologically (VL < 20 copies/ml), 11% still had high VL and 35% had declining VL but did not reach suppression by 6 months on ART. [104]

Nevertheless, many studies do suggest better virological outcomes with earlier start of ART during infancy. One study of incants starting ART within one year of age showed higher rates of viral suppression (<500 copies/mL) by six months in those starting ART in the first three months of life compared to those starting later (63 vs. 19%, p<0.001). Furthermore, it has been shown that a higher number of infants starting ART before six months of age achieved undetectable viral load levels faster over a median follow up time of 4.1 years than infants 6–52 months of age.[2] Evidence from routine care settings prior to the universal ART era for infants living with HIV showed that despite successful treatment of infants starting ART at <6 months of age, a substantial proportion failed to achieve virologic suppression after 6 months on first line treatment and ART initiation characteristics did not significantly predict virologic suppression (<400 copies/ml).[105] Similar poor virologic outcomes were observed from 22 birth identified HIV-positive neonates starting ART in South Africa.[106] These poor levels of viral suppression have been associated with the underdeveloped immune system of infants. Also infants can have very high viral loads and may be slower to suppress as shown among infants on abacavir-based regimens. Poor outcomes are not limited to specific regimens, although poorer outcomes have been recorded with the use of abacavir compared to stavudine.[52]

In terms of longer-term virologic responses, some studies from high-income countries have shown improved long-term virologic control the earlier infants start ART. [77-79, 107] Clinical trials such as the CHER and the PREDICT trials demonstrate good long-term suppression and low rates of change to second-line regimens in children starting immediate ART. Among children in the CHER trial who were virally suppressed on ART for 7–8 years, 75% initiated ART within two months of age relative to 37% who initiated ART within two months of age.

Overall, poor viral suppression among infants is well recognised, however there is limited data describing the trend in viral suppression levels over time, especially among neonates who initiate treatment in the universal ART era. Furthermore, evidence from this review suggests that early ART may be associated with faster time to viral suppression may be associated with low baseline VL and high CD4 when asymptomatic infants are initiated in ART.[108, 109] Nevertheless, the existing evidence is inconclusive. In addition, available evidence of long-term viral suppression at >3 years on treatment are from SSA is limited.

Table 2.2. Literature on viral suppression thresholds and levels among infants starting ART before one year of age in sub-Saharan Africa

Author, year	Country	Study period	Number of children	Median (IQR) age at ART start	Median (IQR) CD4%	Median (IQR) VL at ART start	Timing of VL measurement	VL threshold used	% suppressed
Prendergast, 2008	South Africa			1.2	30 (17–43)	95200 (0.2–3.7 x 10^6)	12 months	400	100
Maswabi, 2020	Botswana	2015-2018	40	2 (1-5)	348 (222–567)	4.05 (IQR, 2.79–4.86)	12 weeks	400	92
Kalawan, 2020	South Africa	2013-2017	91	6 (0-10)	NR	NR	12 months	1000	61.5
Asbjorndottir, 2016	Nairobi and Kenya	2007-2010	121	3.9 (3.3–5.0)	21 (16- 29)	6.6 (6.1-7.0) log copies/ml	6 months	250	32
Ndongo, 2018	Cameroon	2007-2011	190		23.0 (15.0–31.8)	6.5 (5.4–7.0) log copies/ml	24 months	400	78
Porter, 2015	South Africa	2004-2012	4,954	5.9 (3.7-8.7)	18.5 (12 to 26)	NR	6 months	400	28.1
							12 months	400	56.1
Tukei, 2013	Uganda		91	6.2	NR	18%: <5 38%: 5-5.9 44%: >5.9		400	72
Teasdale, 2013	South Africa	2005-2007	269	9.2	18.7	750,000	6 months	400	73
Shiau, 2017	South Africa	2004-2012	1,260	8.7-10.5		NR	6 months	<50	25-49.3 from 3 cohorts
Purchase, 2012	South Africa	2005-2008	129	8.6	15.4 (0.1–43.4)	6.2 (1.4-7.9)	6 months	<50	50
							12 months	<50	57
							6 months	<400	75
							12 months	<400	78

VL: Viral load; WAZ: Weight-for -age-Z-score; Mo: months; NR: Not recorded; IQR: Interquartile range

2.5 What are the determinants of mortality in early treated infants with HIV?

2.5.1 Conceptual framework

The conceptual framework serves as a guide to understand the interplay of the different risk factors affecting survival of children with HIV. It describes the relationship between the exposures (i.e. the different WHO guidelines on infant testing, ART initiation and PMTCT) using the proxy variable for these exposures of ART initiation year, and mortality (outcome). This framework presents the hypothesis that the association between the exposure and the outcome is mediated through changes in characteristics at ART start (patient level characteristics) due to changing ART treatment guidelines that allowed for ART initiation in asymptomatic infants and also through health system level factors such as improved patient management and better ART regimens.

Conceptually, maternal factors such as socioeconomic status were also considered as potential confounders as issues like malnutrition and low socioeconomic status making transport to clinic difficult could impact mortality. Similarly infant (patient) factors such as age and comorbidities such as tuberculosis or severe bacterial infections are also potential confounders as they affect treatment outcomes. However, comorbidities were not explored in the analysis because of incomplete data. The individual level factors of this framework will inform the selection of key variables considered in the analyses. This thesis specifically focuses on the impact of changes in health policies on health outcomes. It will also attempt to understand the relationships between these various factors and how these may change over time as HIV prevention and treatment programs for children are scaled-up across SSA.

Policy-related factors: Health care policy constitutes one of the significant macro-level factors affecting the survival of children living with HIV. The influence of health policies is likely to be indirect; therefore, monitoring population-level outcomes over time is necessary to assess the impact. However, in the absence of a national cohort, collaborative cohort studies can indicate temporal trends attributable to these selected policy changes. Health policies such as the universal ART recommendations and EID guidelines, when adequately implemented, should result in earlier diagnosis and treatment, thereby improving survival among children living with HIV. In addition, with the widespread implementation of Option B+, there is likely to be a shift in the characteristics of infants who still acquire HIV infection. Therefore, health policy changes may impact infant outcomes by a progressive narrowing of the mother-infant population to those with high-risk factors for transmitting and acquiring HIV infection.

Healthcare system-related factors: These include issues associated with paediatric HIV care program and treatment sites such as poor implementation of PMTCT and EID guidelines, poor utilisation of antenatal care and child health services; poor postnatal follow-up of infants exposed to HIV; lack of skilled staff and poor service integration. Many resource-limited country programs lack adequate laboratory and testing facilities. There are also additional health system challenges in providing ART for infants such as the need for liquid formulations (which are very limited), storage requirements for liquid medications (take up a lot more space than tablets and may need refrigeration or at least cool temperature), need for frequent dose adjustments, complexity of clinical management of a very young infant on ART who may have comorbidities. With the declining numbers of new paediatric HIV infections, it also becomes increasingly difficult for healthcare workers who may only manage a few infants to build up experience and expertise in managing this relatively more challenging group of patients.

Furthermore, service integration of PMTCT/EID and paediatric treatment services have been shown to improve retention in care and health outcomes. However, EID tends to be located in PMTCT services which are decentralised, but early infant ART is often offered only in a limited number of facilities. Therefore, infants identified as positive often need to be referred for treatment to a different facility that is further away, increasing the opportunities within the care cascade for the child to become lost to care. Unlike adult HIV testing, PCR is not done as a point of care in most settings, resulting in substantial delays in receipt of infant HIV test results.

Maternal/caregiver-related factors: With widespread PMTCT coverage and dramatic reduction in MTCT, a key population of women living with HIV is emerging; those who transmit the virus to their children despite the HIV care and services in place. Mothers with HIV-positive infants in the era of widespread PMTCT coverage may have challenges related to lack of knowledge of HIV status, stigma and disclosure, lack of transport resources to access health care facilities, poor social circumstances and marginalisation all of which could lead to poor retention on ART. In addition, MTCT in the era of widespread ART may be an indicator of challenges with accessing treatment and being retained in care, treatment adherence and care-seeking attitude in women living with HIV. These challenges would likely influence the approach to care for their HIV-positive infants and consequently health outcomes.

Infant-related factors: Infants born to this critical group of women with HIV described above have various characteristics that may influence their survival on ART. As the number of new paediatric HIV infections decreases, a higher proportion of infants with HIV may have risk factors associated with poorer survival on ART. These risk factors include low birth weight, prematurity at birth, congenital infections, and other infectious comorbidities requiring more complex management. Healthcare workers with specialized skills for this complex management are often unavailable in resource-limited settings, especially in more remote areas. Demographic factors such as age at ART initiation play an important role since EID coverage has increased and allowed vulnerable infants who would have died before identification to initiate ART. Clinical factors at ART initiation such as viral load, nutritional status and clinical disease stage are crucial factors associated with survival.

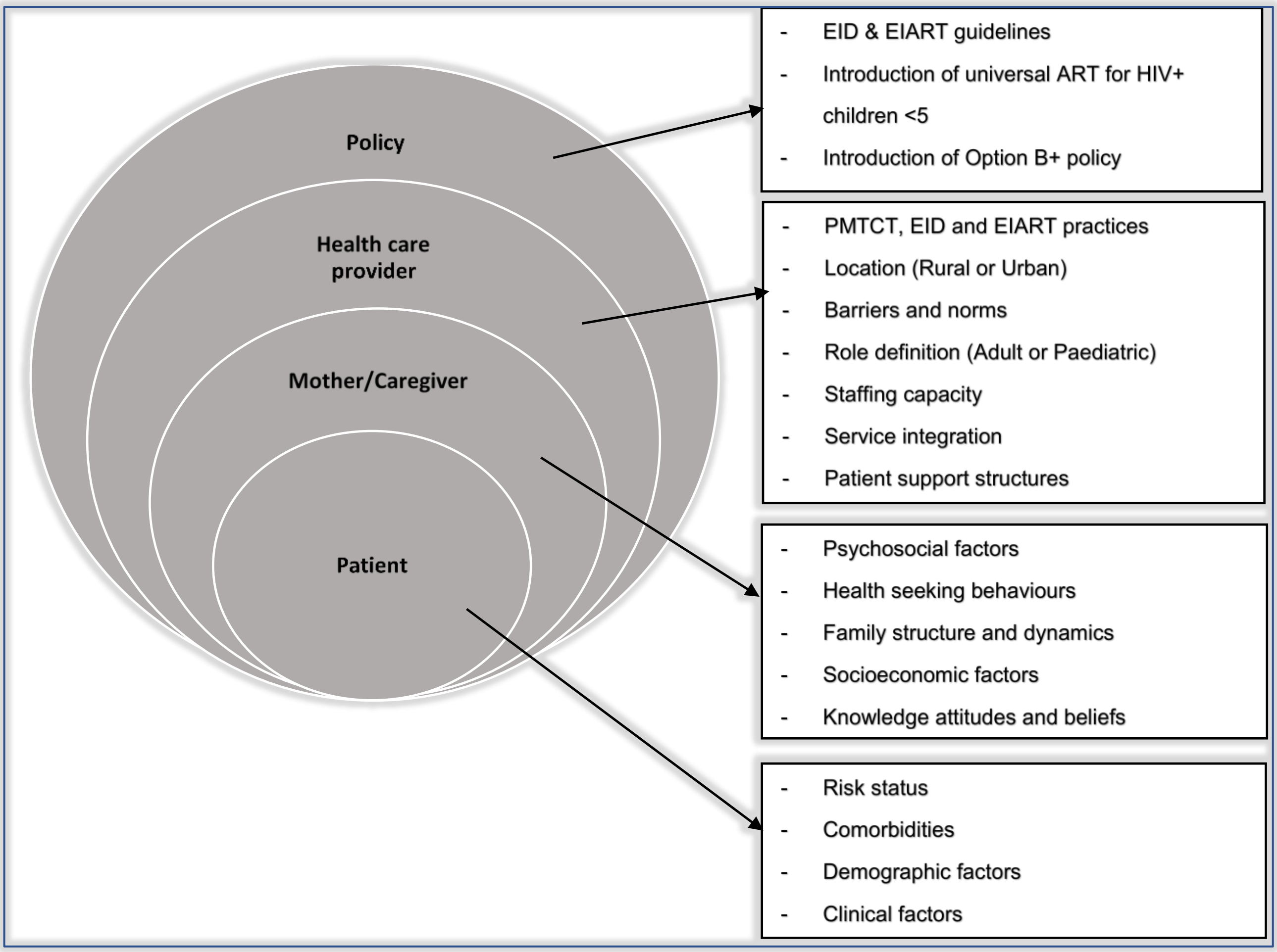

Figure 2-1. Multilevel factors influencing the survival of infants and young children living with HIV *PMTCT: Prevention of mother -to child- transmission of HIV; EID: Early infant diagnosis; EIART: Early infant antiretroviral therapy

2.5.2 *Health state at ART initiation*

Risk factors for mortality among children with HIV have been extensively described. However, there is less evidence about risk factors for children initiating ART after implementation of Option B+. Younger age (<2 years), underweight (WAZ <-2) and severe immune suppression are established risk factors for mortality among infants and young children.[48, 49, 66, 67, 92, 110-112]. Infants <1 year of age have 2-12 times higher mortality compared to older children.[61, 89] Another study enrolling children <15 years of age from four African HIV programmes between 2001-2010 observed higher mortality in infants compared to older children, with the lowest mortality observed in the 2–4-year age category. This low mortality may have been due to survival bias, as this group would exclude the sickest children who had experienced early death before ART initiation due to rapid disease progression. [18] Another study also showed a high probability of mortality among infants receiving ART as early as five months of age. [33] One study conducted in Malawi showed similar disproportionate mortality among children <1 year of age.[15] High mortality in infants has been associated with late initiation of ART due to EID challenges, as observed in evidence from RLS. This is supported by the finding that in children <5 years of age, severe wasting (WAZ ≤-3.0) was also associated with increased mortality risk.[19]

Data on the association between maternal and child health ART outcomes is widespread. Poor maternal health leads to an increased risk of MTCT, rapid disease progression and death in infants. There are maternal factors that have been identified as risk factors of mortality among children living with HIV. In a study of South African infants with HIV (median age 5.4 months) enrolled into care in 2011, maternal CD4 ≤350 cells/ µl or no maternal ART was related with increased mortality risk. Also, children with PMTCT exposure were less likely to die and have higher CD4% at ART initiation, despite having higher VL.[46] There is a need for careful consideration when interpreting these results. Children infected despite PMTCT exposure are likely to have acquired the infection in utero before PMTCT regimens were started and thus have been infected for longer and have higher VL.

There may be changes over time in the individual risk factors of mortality considering that infants may be starting ART with better health status due to early diagnosis before the onset of severe disease. In contrast to most previous studies, a study in 2011 assessed six months post enrolment mortality among 272 infants enrolled in care at ≤24 months of age in South Africa and found that child age at enrolment was not predictive of mortality.[46] It is important to note that this study assessed mortality after enrolment in care and not post ART initiation. There are almost no observational studies describing post ART initiation mortality among infants with HIV starting ART after 2013. Diagnosis during hospital admission has been associated with increased mortality compared to those diagnosed through PMTCT programs.[46, 54] This may be due to the fact that those diagnosed through PMTCT programmes are potentially asymptomatic and younger compared to those diagnosed during a hospital admission who are likely sicker, possibly older and have caregivers who may not be linked and followed up in the health system.[46] Therefore, there is a need to focus on other entry points such as hospital and nutrition wards for diagnosis and EIART as infants in these contexts have a higher risk of poorer outcomes without timely ART initiation.

2.5.3 Calendar year of ART Initiation

A few observational studies that include large cohorts of infants and young children living with HIV in SSA have assessed temporal trends in mortality, but findings remain inconsistent. In children initiating HIV treatment between 2001-2010 in four programmes, mortality hazards were higher among children starting ART in the earliest period between 2001–2004 compared to 2008–2010. This early period was before the ART was available at all national programs and characterised by very limited ART access which likely explains the higher mortality reported. [92] In contrast another study demonstrated that children from West Africa starting ART before 2005 had reduced mortality and LTFU compared to children starting treatment in 2005 (aHR LTFU 1.7, 95% CI:1.3–2.4) and during or after 2006 (aHR LTFU 3.0, 95%CI 2.2–4.0) (p<0.01). [89] Given limited ART access prior to 2005, children initiating ART in this period were likely highly selected survivors who had already demonstrated good prognosis and been retained in care for several months or years prior to ART initiation.

While there is a clear improvement in mortality and LTFU compared to the pre-ART era, the evidence of improved mortality and LTFU over time is less consistent in recent years. A study conducted in SSA that included 17,712 children with HIV aged 0-15 at ART initiation from 2005-2011 found no significant evidence for reduced LTFU or mortality by year of ART initiation. [61] A more recent study of children <15 years of age initiating ART in South Africa found more rapid loss from programme in most recent years with 26% of children initiated on ART after August 2012 lost within a year of ART start compared to 14% among children started on ART prior to April 2010 [hazard ratio (HR) 2·0, P< 0·001). This trend was more obvious among infants; among infants initiated on ART after August 2012, 15% more were lost within the first year on ART than among infants initiating ART before April 2010.[113] Nonetheless it is reassuring that a temporal trend of decreasing risk in mortality among older children has been observed, suggesting that ART may be started in a more timely manner in recent years.[67, 71, 82]

Among infants living with HIV, evidence suggests an improvement in program outcomes over time. A cohort study of 4945 infants initiating ART before one year of age in Southern Africa from 2004-2012 showed reduced mortality from the beginning of 2010 onwards after adjusting for other demographic and clinical characteristics at ART initiation. This observed improvement may have resulted from WHO guidelines for immediate ART that resulted in earlier ART initiation in infants and could have improved attention and care for infants with HIV.[48]

2.5.4 Program and facility-level determinants

One of the challenges with the scale-up of ART includes the increased burden on the already strained healthcare systems in under-resourced countries. Given that infants with HIV are a small group compared to the huge population requiring immediate ART, they may get overlooked in the context of efforts to achieve 90-90-90 for all adults and children. HIV diagnosis and treatment among infants is complicated and may require relatively more resources than other groups to achieve the 90-90-90 target. Therefore, while universal ART is being scaled up, there is a need for specific attention for infants with HIV. There are very few studies that account for characteristics of health facilities and programmes and their impact on mortality and LTFU of infants in the context of widespread ART. While one study found mortality was associated with facilities being located in rural areas,[114] another study showed no significant impact of facility-level factors on the risk of LTFU or death. [61] Factors such as higher staff capacity, shorter wait times, and more active patient follow-up have been shown to decrease mortality and LTFU in children significantly. [61]

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Chapter 3: Variations in the characteristics and outcomes of children living with HIV following universal art in sub-Saharan Africa (2006–17): a retrospective cohort study

Relevance of this paper to the thesis:

This manuscript assessed the effect of expansion of ART eligibility guidelines on the characteristics and outcomes of young children starting ART within five years of age in sub-Saharan Africa. This chapter examined the trends in uptake of early infant ART in the region (by assessing the proportion of infants starting ART <3 months of age), characteristics of children starting ART and outcomes including mortality and loss to follow-up. These analyses address the gap in literature by describing patterns in characteristics and outcomes over a 12 year period of guideline changes among young children under 5 years of age.

Contribution of the student and co-authors:

I conceptualised the analysis with guidance from MD. I conducted all the statistical analyses and interpreted the results with critical input from all co-authors. I wrote the first draft of the manuscript. All co-authors commented on drafts of the manuscript and approved the final version for submission.

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Variations in the characteristics and outcomes of children living with HIV following universal ART in sub-Saharan Africa (2006–17): a retrospective cohort study

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Summary

Background The proportion of children living with HIV and receiving antiretroviral therapy (ART) in sub-Saharan Africa has increased greatly since 2006, yet the changes in their demographic characteristics and treatment outcomes have not been well described. We examine the trends in characteristics and outcomes of children living with HIV who were younger than 5 years at ART initiation, and compare outcomes over time and across country income groups.

Methods We conducted a retrospective cohort analysis of data from children living with HIV who were younger than 5 years at ART initiation from 45 paediatric sites in 16 low-income, lower-middle-income, and upper-middle-income countries in sub-Saharan Africa (Benin, Burundi, Côte d'Ivoire, Democratic Republic of the Congo, Ghana, Kenya, Lesotho, Malawi, Mali, Mozambique, Rwanda, South Africa, Togo, Uganda, Zambia, and Zimbabwe). Outcomes were trends in patient characteristics at ART initiation (age, weight, height, and CD4%), and comparisons of mortality and loss to follow-up during ART over time and in various economic settings. We identified risk factors for mortality using Cox proportional hazards models. Each participating region had relevant institutional ethics review board approvals to contribute data to the analysis.

Findings We included 32 221 children living with HIV and initiating ART younger than 5 years between Jan 1, 2006, and Dec 31, 2017. Median age at ART initiation was 20·4 months (IQR 9·4–36·0) in 2006–10, 19·2 months (8·3–33·6) in 2011–13, and 19·2 months (8·8–33·7) in 2014–17. Median age at ART initiation was 13·2 months (IQR 4·7–26·8) in upper-middle-income countries, 22·6 months (13·2–37·5) in lower-middle-income countries and 24·2 months (13·5–39·1) in low-income countries. The proportion of children initiating ART younger than 3 months increased from 770 (5·1%) of 14 943 children in 2006–10 to 728 (10·0%) of 7290 children in 2014–17. The proportion of children initiating ART with severe immunosuppression decreased from 5469 (74·7%) of 7314 children for whom CD4% data were available in 2006–10 to 2353 (55·2%) of 4269 children in 2014–17. Mortality at 24 months on ART decreased from 970 (6·5%) of 14 943 children in 2006–10 to 214 (2·9%) of 7290 children in 2014–17. Loss to follow-up was 20·5% (95% CI 20·1–21·0) overall, and was similar across time periods. In multivariable analysis, lower mortality was observed for more recent ART initiation cohorts (adjusted hazard ratio 0·70, 95% CI 0·63–0·79 for 2011–13; 0·53, 0·45–0·72 for 2014–17 *vs* 2006–10) and for those residing in an upper-middle-income country (0·42, 0·35–0·49 *vs* low-income countries).

Interpretation Mortality declined significantly after universal ART recommendations for children younger than 2 years in 2010 and children younger than 5 years in 2013. However, substantial variations persisted across country income groups, and one in five children continue to be lost to follow-up. Targeted interventions are required to improve outcomes of children living with HIV, especially in the poorest countries.

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*Members of the IeDEA Collaboration in participating regions are listed in the appendix (pp 6–9)

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Introduction

Sub-Saharan Africa is home to approximately 80% of the 1·8 million children living with HIV globally.[1] Several milestone achievements in paediatric HIV care, prevention, and treatment have been realised since 2006, including improved paediatric antiretroviral therapy (ART) regimens, the introduction of universal ART for all children younger than 5 years regardless of clinical and immunologic status,[2,3] and scale-up of early infant diagnostic and treatment programmes. However, progress in the expansion of these improved HIV care and treatment services remains highly varied across sub-Saharan Africa. Without updated data on the trends in the characteristics of children at ART initiation and their survival and related outcomes, the effect of the WHO universal ART guidelines[3] remain unclear.

According to UNAIDS estimates, ART coverage among children younger than 14 years increased from 25% to 59% in east and southern Africa between 2010 and 2017, compared with an increase from 8% to 26% in west and

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Research in context

Evidence before this study

We searched PubMed from Jan 1, 2006, to July 31, 2019, using combinations or variations of the following search terms: "HIV", "antiretroviral therapy", "children" "mortality" and "loss to follow-up". Searches were limited to articles published in English. The introduction of antiretroviral therapy (ART) has transformed the survival of children living with HIV. Access to and coverage of paediatric ART has increased since 2006, but with substantial variations across regions in sub-Saharan Africa. Several observational studies have described outcomes of children living with HIV from single cohorts and in the pre-ART era. However, less is known about the effect of expansions in paediatric ART eligibility guidelines and services for young children living with HIV across sub-Saharan Africa, especially among those who acquired HIV in the era of improved prevention of mother-to-child transmission and ART programmes. Furthermore, we did not find any studies that compared outcomes of young children living with HIV across economic settings.

Added value of this study

This multiregional study presents a unique opportunity to improve our understanding of the effect of expanding paediatric ART eligibility guidelines and services on the outcomes of young children living with HIV across sub-Saharan Africa since 2006. The expansion of universal ART for children in large-scale ART programmes is reflected by an improvement in the health status of children starting ART and by decreasing mortality. High mortality risk, particularly among underweight children and those in lower-middle-income countries, remains a challenge that requires specific focus.

Implications of all the available evidence

Although the inequalities in mortality improvement among children living with HIV in sub-Saharan Africa warrant further investigation, findings suggest a positive effect of efforts to implement universal treatment. However, loss to follow-up remains a challenge that undermines the success of ongoing interventions. There is a need to increase focus on targeted approaches for improved paediatric HIV programme uptake of early diagnosis, early ART initiation and retention in care for children living with HIV in resource-limited settings.

central Africa.[1] In high burden, resource-constrained settings, serious barriers to expansion of paediatric HIV care remain, including delayed diagnosis, poor linkage to care among those diagnosed, late ART initiation, low access to free HIV services for children, and poor retention in care.[4] As a result, the scale-up of routine paediatric care programmes in sub-Saharan Africa continues to lag behind adult HIV care.[5] Even where children living with HIV are identified early and started on treatment immediately, they continue to have poorer outcomes compared with their adult counterparts.[1,6–8] The median age of children starting ART, a surrogate of earlier diagnosis, is declining. Yet many still present with advanced disease and remain at a high risk of early death or attrition.[9–13] In a systematic review of 30 000 children younger than 10 years living with HIV, 5–29% of children had died or were lost to follow-up within 12 months of ART initiation.[14] Interpretation of these poor treatment outcomes in routine care settings is further hampered due to high rates of loss to follow-up, with no mortality ascertainment in those lost.[5] Studies assessing the outcomes of young children living with HIV over time and across economic settings are also scarce.

For more on **IeDEA** see https://www.iedea.org/

Therefore, as efforts to improve effective paediatric HIV diagnosis and ART programmes go on across sub-Saharan Africa, we need to assess the effect of changing treatment guidelines and programme scale-up on the outcomes of children living with HIV, to ensure equity in outcomes. We used data from four International epidemiologic Databases to Evaluate AIDS (IeDEA) regions in Africa to describe the temporal trends in characteristics of children younger than 5 years initiating ART, and to compare outcomes over time and across country income groups.

Methods

Data sources and population

IeDEA is an international research consortium of HIV care and treatment sites in 46 countries across seven world regions, which was established to evaluate outcomes of people living with HIV by using retrospective and prospective data collated in a standard format. IeDEA patient data are collected in all regions during routine clinic visits at ART initiation and at each follow-up visit. Using a standard IeDEA multiregional data transfer format, regional data centres sent deidentified data to the University of Cape Town, South Africa for cleaning and analysis.

We did a retrospective cohort analysis of data from 45 IeDEA paediatric cohorts from 16 countries across east Africa (Kenya and Uganda), west Africa (Benin, Côte d'Ivoire, Ghana, Mali, and Togo), central Africa (Burundi, Democratic Republic of the Congo, and Rwanda), and southern Africa (Lesotho, Malawi, Mozambique, South Africa, Zambia, and Zimbabwe). Eligible patients were children with HIV who started combination ART comprising three antiretroviral drugs from at least two drug classes at younger than 5 years. Each participating IeDEA region had relevant institutional ethics review board approvals to contribute data to this analysis.

Procedures and outcomes

The primary outcomes of interest were trends in patient characteristics (age, weight, height, and CD4%) at initiation of ART, and mortality within 24 months of initiation of ART. Secondary outcomes were loss to follow-up and transfer out of care within 24 months of ART initiation. Participants were followed up from ART initiation until death, loss to follow-up, transfer out of care, or 24 months of treatment. We defined mortality as all-cause mortality as documented by the clinical site (specific causes of death were not available). We further categorised mortality into early (<6 months from initiation of ART) and late (6–24 months from initiation of ART). Transfer out of care was defined as a documented transfer to a different clinical site, and loss to follow-up was defined as no clinic or laboratory visit for more than 365 days before database closure for each cohort. We administratively censored children who were lost to follow-up on the date of last clinic visit. Age and sex-specific weightfor-age Z score (WAZ) and height-for-age Z score (HAZ) were calculated using the 2007 WHO growth reference standards.[15] We defined underweight as WAZ less than –2 and stunted growth as HAZ less than –2. For WAZ, HAZ, and CD4 values (cell count and %) at initiation of ART, we used the measurements taken closest to ART start date (within 3 weeks before and 1 month after ART initiation). Severe immunosuppression was defined as CD4% less than 20% for children aged up to 12 months and less than 15% for children aged 13–59 months, as per WHO 2006 criteria.[16]

Children were grouped into three cohorts according to their calendar year of ART initiation (2006–10, 2011–13, and 2014–17) to estimate the effect of changes in the WHO ART and prevention of mother-to-child transmission of HIV (PMTCT) guidelines. In 2008,[17] WHO interim guidance recommended immediate ART regardless of clinical or immunologic status for all children younger than 12 months living with HIV. Universal ART was extended to all children younger than 2 years in 2010[18] and children younger than 5 years in 2013.[17,19] In 2013, all pregnant and breastfeeding women living with HIV were eligible for ART, an increase from previous CD4 and disease severity eligibility criteria.[17]

We assigned country income groups according to the World Bank country income allocation[20] in the median year of ART initiation for children in each country (low-income country, lower-middle-income country, or upper-middle-income country). Low-income countries included 28 cohorts from Benin, Burundi, Democratic Republic of Congo, Kenya, Malawi, Mali, Mozambique, Rwanda, Togo, Uganda, and Zimbabwe; lower-middle-income countries included eight cohorts from Côte d'Ivoire, Ghana, Lesotho, and Zambia; and upper-middle-income countries included nine cohorts from South Africa. Geographical region allocation was according to IeDEA regions including 16 cohorts from central Africa, four from east Africa, 17 from southern Africa and nine from west Africa.

Statistical analysis

We described patient characteristics at ART start as frequency and % (categorical variables), and as medians and IQR (continuous variables). These characteristics were compared by ART initiation cohort using the Kruskal-Wallis test for continuous variables and $\chi 2$ or Fisher's exact test for categorical variables. Using competing risk analyses, overall and by ART initiation period and country income groups, we calculated cumulative incidence functions for mortality, loss to follow-up, and transfer out of care. We considered loss to follow-up and transfer out of care as competing risks when death was the outcome. Similarly, we considered death and transfer out of care as competing events when the outcome was lost to follow-up. We further compared the risk of mortality across country income groups and ART initiation cohorts using Cox proportional hazards models. Explanatory variables in the models included sex, age at ART initiation, year of ART initiation, region, country income groups, immunosuppression status, HAZ, and WAZ.

The true outcomes of children who were defined as lost to follow-up in this study were unknown. The heterogeneity of settings and the variability of mortality under-ascertainment between settings make comparability of mortality estimates challenging. Studies[21–23] reporting tracing outcomes of children in sub-Saharan Africa have shown that 11–38% of children categorised as lost to follow-up had actually died. To evaluate the effect of potential bias due to loss to follow-up on mortality, we did a sensitivity analysis by assuming that varying proportions (10%, 30%, 50%, and 100%) of children lost to follow-up had died. We calculated cumulative incidences and unadjusted mortality hazard ratios for the varying scenarios and compared them with the overall estimates.

We used multiple imputation to impute missing baseline CD4 values (cell count and %) and weight measurements. For the imputation models, we assumed data were missing at random. All baseline variables were included, as were outcomes of mortality and follow-up time, and ten imputation sets were generated. All analyses were done using Stata version 15.0 (StataCorp, College Station, TX, USA).

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 32 221 children with HIV aged younger than 5 years at ART initiation between Jan 1, 2006, and Dec 31, 2017, from 16 low-income countries, lower-middle-income countries, and upper-middle-income countries in sub-Saharan Africa (table 1). 49·1% of the included children were female and 75·8% were from the IeDEA southern Africa region. 10 117 (74·5%) of children were enrolled from urban or semi-urban sites, 24004 (31·4%) were enrolled from tertiary facilities, and 12759 (39·6%) were enrolled from sites with academic affiliations. The number of children initiating ART halved from 14943 in 2006–10 to 7290 in 2014–17.

Median age at ART initiation across calendar periods remained stable, at 20·4 months (IQR 9·5–36·0) in 2006–10, 19·2 months (8·3–33·6) in 2011–13, and 9·2 months (8·8–33·7) in 2014–17. However, the proportion of children initiating treatment younger than 3 months was twice as high in 2014–17 (728 [10·0%] of 7290 children) than in 2006–10 (770 [5·1%] of 14943 children; table 1). Median CD4% at the start of ART increased from 16% (IQR 11–22%) in 2006–10 to 20% (13–28) in 2014–17.

	Total	2006–10	2011–13	2014–17
Population (n)	32221	14943	9988	7290
Region				
Central Africa	707 (2·2%)	383 (2·5%)	215 (2·2%)	109 (1·5%)
East Africa	5044 (15·7%)	1947 (13·0%)	1896 (18·9%)	1201 (16·4%)
Southern Africa	24410 (75·8%)	11440 (76·7%)	7274 (72·8%)	5696 (78·1%)
West Africa	2060 (6·4%)	1173 (7·8%)	603 (6·0%)	284 (3·9%)
Country income group				
Low income	11510 (35·7%)	4485 (30·0%)	4273 (42·7%)	2752 (37·7%)
Lower-middle income	8252 (25·6%)	3642 (24·3%)	2291 (22·9%)	2319 (31·8%)
Upper-middle income	12459 (38·6%)	6816 (47·6%)	3424 (34·2%)	2219 (30·4%)
Sex				
Female	16101 (49·1%)	7335 (49·1%)	5031 (50·4%)	3754 (51·5%)
Male	16120 (50·0%)	7608 (50·9%)	4957 (49·6%)	3536 (48·5%)
Median age, months	20·4 (8·3 to 34·8)	20·4 (9·5 to 36·0)	19·2 (8·3 to 33·6)	19·2 (8·8 to 33·7)
Age category				
0–3 months	2207 (6·8%)	770 (5·1%)	709 (7·1%)	728 (10·0%)
4–12 months	7933 (24·6%)	3791 (25·4%)	2518 (25·2%)	1624 (22·3%)
13–36 months	14505 (45·0%)	5093 (44·9%)	4762 (44·9%)	4650 (45·2%)
37–60 months	7576 (23·5%)	2874 (25·3%)	2431 (22·9%)	2271 (22·0%)
Median CD4%	17% (11 to 24%)	16% (11 to 22%)	18% (12 to 26%)	20% (13 to 28%)
Median CD4 count, cells per µl	708 (380 to 1181)	625 (333 to 1030)	756 (404 to 1227)	826 (450 to 1378)
Severely immunosuppressed*				
No	6096 (34·3%)	1845 (25·2%)	2335 (37·6%)	1916 (44·8%)
Yes	11680 (65·7%)	5469 (74·7%)	3860 (62·3%)	2353 (55·2%)
Missing	14445	4026	4411	6015
Median WAZ	–1·8 (–3·2 to –0·7)	–2·1 (–3·4 to –0·9)	–1·8 (–3·2 to –0·7)	–1·6 (–2·9 to –0·4)
WAZ category*				
≤–3	6839 (28·6%)	2891 (32·8%)	2243 (27·7%)	1705 (24·1%)
>–3 to ≤–2	4514 (18·8%)	1783 (20·2%)	1538 (19·0%)	1193 (16·9%)
>–2	12548 (52·4%)	4123 (46·8%)	4289 (53·1%)	4136 (58·8%)
Missing	8329	2543	2536	3250
Median HAZ	–2·5 (–3·8 to –1·3)	–2·7 (–3·9 to –1·5)	–2·5 (–3·7 to –1·5)	–2·3 (–3·7 to –0·9)
HAZ category*				
≤–3	7470 (40·8%)	3023 (43·9%)	2482 (36·1%)	1965 (37·4%)
>–3 to ≤–2	3902 (21·3%)	1473 (21·4%)	1318 (21·3%)	1111 (21·1%)
>–2	6917 (37·8%)	2378 (34·5%)	2370 (38·4%)	2169 (41·3%)
Missing	13941	4466	4436	5039
Outcome				
Retained	20160 (62·6%)	9924 (66·4%)	5912 (59·2%)	4324 (59·3%)
Death	1654 (5·1%)	970 (6·5%)	470 (4·7%)	214 (2·9%)
Lost to follow-up	7441 (23·0%)	2649 (17·7%)	2518 (25·2%)	1534 (21·0%)
Transfer out of care	2966 (9·2%)	1400 (9·3%)	1088 (10·8%)	478 (6·5%)

*Calculated as a percentage of those participants for whom data were available; see Results for more details. Data are n (%) or median (IQR) unless otherwise specified. χ^2 test used for categorical variables and Kruskal-Wallis test used for continuous variables. HAZ=Height-for-age Z-score. WAZ=Weight-for-age Z-score.

***Table 1:* Characteristics and outcomes of children living with HIV in sub-Saharan Africa by year of antiretroviral therapy initiation**

Among children with available CD4 cell count and % data, the proportion of severely immunosuppressed children at the start of ART decreased from 5469 (74·7%) of 7314 in 2006–10 to 2353 (55·2%) of 4269 children in 2014–17. The proportion of children severely underweight at ART initiation (WAZ ≤–3) decreased gradually from 2891 (32·8%) of 8814 children for whom data were available in 2006–10, to 1705 (24·1%) of 7034 children for whom data were available in 2014–17. However, the proportion of children with severely stunted growth at ART initiation (HAZ ≤–3) remained fairly stable, at 3023 (43·9%) of 6874 children for whom data were available in 2006–10 and 1965 (37·4%) of 5245 children for whom data were available in 2014–17 (table 1). According to country income groups, median age at ART initiation was lowest in upper-middle-income countries (13·2 months, IQR 4·7–26·8 in upper-middle-income countries; 24·2 months, 13·5–39·1 in low-income countries; and 22·6 months, 13·3–37·5 in lower-middle-income countries; appendix p 1). 5908 (47·4%) of 12 459 children in upper-middle-income countries were younger than 12 months at ART initiation, compared with 1732 (20·9%) of 8252 children in lower-middle-income countries and 2500 (21·7%) of 11 510 children in low-income countries. The proportion of children who were severely immunosuppressed, underweight, or had stunted growth at ART initiation was similar between country income groups (appendix p 1).

1654 (5·1%) of 32 221 children died, 7441 (23·0%) were lost to follow-up, and 2966 (9·2%) had transferred out to other facilities within 24 months of ART. The number of children who died within 24 months of ART initiation decreased from 970 (6·5%) of 14 943 children in 2006–10, to 214 (2·9%) of 7290 children in 2014–17 (table 1). The cumulative incidence estimates by 24 months on ART were 5·1% for death (95% CI 4·8–5·3), 20·5% for loss to follow-up (20·1–21·0), and 9·2% for transfer out of care (8·8–9·5). Children starting ART aged between 4 and 12 months had the highest cumulative incidence of death compared with children aged 3 months or younger, children aged 13–36 months, or children aged 37–60 months (figure 1). Children residing in west Africa had the highest mortality of the geographical regions (10·6%, 95% CI 9·3–12·0), with central Africa recording the lowest (2·9%, 1·8–4·4). Mortality was lowest in upper-middle-income countries (3·3%, 95% CI 3·0–3·6; 6·7%, 6·2–7·2 in lower-middle-income countries; 5·8%, 5·4–6·3 in low-income countries; appendix p 2). Loss to follow-up by 24 months on ART was also lowest in upper-middle-income countries (14·3%, 95% CI 13·7–15·0; 28·6%, 27·6–29·5 in lower-middle-income countries; 21·5%, 20·8–22·3 in low-income countries; appendix p 2). Loss to follow-up ranged from 16·7% (95% CI 15·1–18·3) in west Africa to 21·6% (20·5–22·8) in east Africa (appendix p 2)

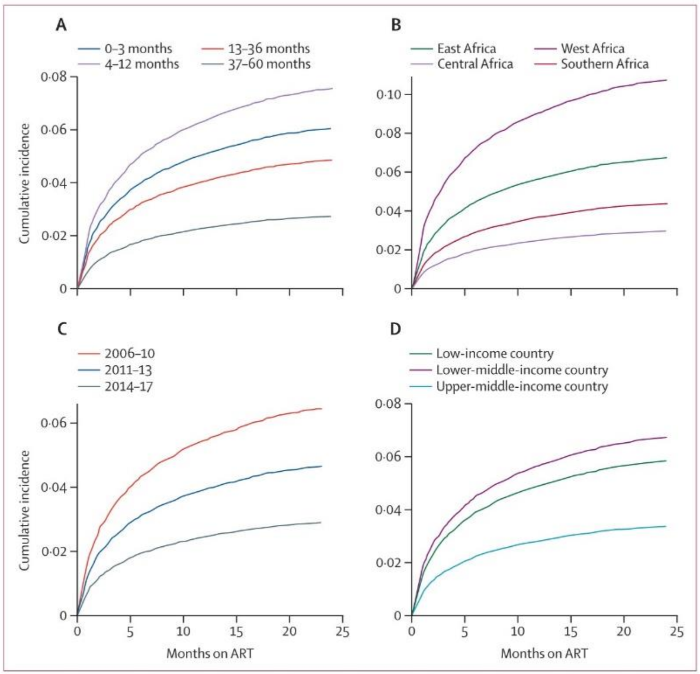

Figure 1: **24-months cumulative incidence of mortality in the first 24 months of ART in children younger than 5 years at ART initiation in sub-Saharan Africa**
(A) Mortality incidence by age at ART initiation. (B) Mortality incidence by geographical region (C) Mortality incidence by year of ART initiation. (D) Mortality incidence by country income group. ART=antiretroviral therapy.

Death occurring before loss to follow-up or transfer out of care decreased over time, with cumulative incidence 6·4% (95% CI 6·1–6·8) in 2006–10 and 2·9% (2·5–4·3) in 2014–17. This pattern was consistent across country income groups, with a marked decrease in mortality after 2010 in lower-middle-income countries (figure 2A). Loss to follow-up remained stable, with overall cumulative incidence 17·7% (95% CI 17·1–18·3) in 2006–10, 24·5% (23·7–25·4) in 2011–13, and 21·0% (20·1–21·9) in 2014–17. The observed pattern was similar across country income groups. However, lower-middle-income countries recorded the most loss to follow-up in all calendar periods, and we observed a marked increase in loss to follow-up in upper-middle-income countries after 2010 (figure 2B). 1091 (66%) of 1654 deaths occurred in the first 6 months after ART initiation (early death). The proportion of children who died within 6 months of ART initiation was lower in children starting ART in 2014–17 (134 [62·6%] of 214 deaths), compared with the 2006–10 cohort (675 [69·6%] of 970 deaths, p=0·019). There was no significant difference in the pattern of early death by country income group (p=0·220) or age at ART initiation (p=0·291; data not shown).

See Online for appendix

In multivariable analysis (adjusted for sex, age at ART initiation, year of ART initiation, geographical region,

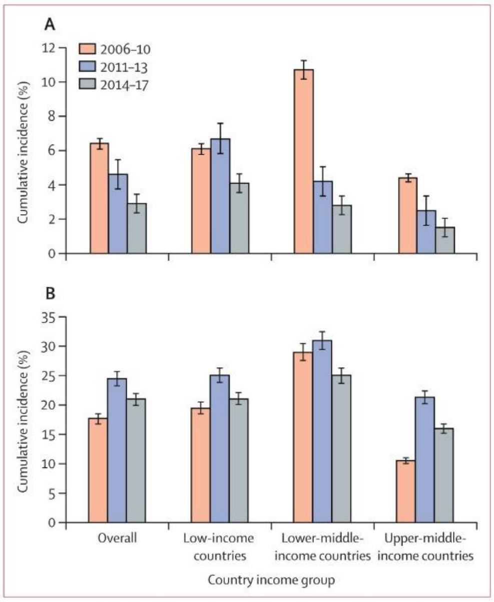

***Figure 2:* Cumulative incidence of mortality and loss to follow-up in the first 24 months of ART in children younger than 5 years at ART initiation by country income group**

(A) Mortality in the first 24 months of ART by country income group with loss to follow-up and transfer out as competing events. (B) Loss to follow-up in the first 24 months of ART by country income group with mortality and transfer out as competing events. Range bars indicate 95% CI. ART=antiretroviral therapy.

	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
ART initiation year		
2006–10	1	1
2011–13	0·74 (0·71–0·77)	0·70 (0·63–0·79)
2014–17	0·52 (0·49–0·56)	0·53 (0·45–0·62)
Country income group		
Low income	1	1
Lower-middle income	1·19 (1·13–1·24)	1·26 (1·09–1·44)
Upper-middle income	0·55 (0·52–0·58)	0·42 (0·35–0·49)
Region		
East Africa	1	1
West Africa	1·68 (1·57–1·80)	1·11 (0·92–1·34)
Central Africa	0·40 (0·30–0·48)	0·40 (0·26–0·63)
Southern Africa	0·67 (0·64–0·71)	0·71 (0·61–0·84)
Age at ART initiation (months)		
0–3	1	1
4–12	1·15 (1·07–1·24)	0·75 (0·61–0·91)
13–36	0·70 (0·65–0·76)	0·38 (0·31–0·46)
37–60	0·37 (0·34–0·40)	0·23 (0·18–0·28)
Sex		
Male	1	1
Female	0·91 (0·88–0·95)	0·99 (0·90–1·09)
Severely immunosuppressed		
No	1	1
Yes	2·03 (1·94–2·13)	1·54 (1·30–1·82)
WAZ		
>–2	1	1
>–3 to ≤–2	1·80 (1·69–1·92)	1·72 (1·47–2·01)
≤–3	3·45 (3·30–3·61)	3·16 (2·82–3·54)

*Multivariable analysis was adjusted for sex, age at ART initiation , year of ART initiation, geographical region, country income group, immunosuppression status, and WAZ. Models were imputed for missing CD4% and WAZ at antiretroviral therapy initiation. ART=antiretroviral therapy. WAZ=weight-for-age Z score.

***Table 2:* Hazard ratios of mortality among children younger than 5 years at ART initiation in sub-Saharan Africa**

countriy income group, immunosuppression status, and WAZ), adjusted hazard ratio (aHR) for death was lower for children starting ART in 2014–17 (aHR 0·53, 95% CI 0·45–0·62) and 2011–13 (0·70, 0·63–0·79), compared with 2006–10, and lower for participants living in an upper-middle-income country compared with a low-income country (0·42, 0·35–0·49). Risk factors associated with increased mortality included living in lower-middle-income countries (aHR 1·26, 95% CI 1·09–1·44), severe immunosuppression at ART initiation (1·54, 1·30–1·82), and underweight (1·72, 1·47–2·01; table 2). In a model stratified by age category at ART initiation (ie, 12 months or younger, 13–36 months, and 37–60 months), mortality risk decreased over time in all age groups. However, mortality risk was much greater for children aged 13–36 months and 37–60 months at ART initiation than with children aged 12 months or younger at ART initiation (see Discussion). Children staring ART between the ages of 13 and 36 months in lower-middle-income countries had a higher risk of mortality compared with those in a low-income country (aHR 1·36, 95% CI 1·11–1·66; table 3). The patterns of mortality observed in models with imputed missing data were similar to estimates from models using complete case data (appendix pp 3–4).

In a sensitivity analyses that assumed the worst-case scenario that 100% of children lost to follow-up had died, the cumulative incidence of mortality after 24 months on ART was 25·7% (95% CI 25·2–26·2), which is 5 times higher than our observed mortality (appendix p 5). In addition, the observed relative decreases in mortality hazards over time were attenuated. However, even if we assumed that all loss to follow-up was due to mortality, children initiating ART in upper-middle-income countries still had the lowest risk of mortality relative to low-income countries (aHR 0·64, 95% CI 0·59–0·68; table 4, appendix p 5).

Discussion

In this multiregional cohort of more than 32 000 children living with HIV in sub-Saharan Africa and starting ART younger than 5 years, we present findings on the demographics and treatment outcomes across time periods and country income groups. The proportion of children starting ART at younger than 3 months between 2014 and

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2017 was double the proportion in 2006–10, while underweight and severe immune suppression in children at ART initiation decreased over the same period. Children initiating ART in 2014–17 had half the mortality risk of those initiating ART in 2006–10, and mortality was lowest in upper-middle-income countries. However, loss to follow-up remained unchanged, with one in five children lost before 2 years on ART. Assuming a wide range of possible proportions of unascertained mortality in all children lost to follow-up, the risk of death remained substantially lower in upper-middle-income countries than in low-income countries; however, the improvement in mortality for children initiating ART in 2014–17 compared with children starting in 2006–10 was erased if more than half of children lost to follow-up were assumed to have died.

We found similar median ages at ART initiation across cohorts. This might be due to restriction of our study population to children younger than 5 years at treatment initiation, by contrast with other studies that suggested a decline in age at ART start in children younger than 16 years with HIV.[6,7] In addition, the overall reduction in the absolute number of new paediatric HIV infections could be a contributing factor, as there are fewer younger children needing to start ART overall. Nonetheless, the proportion of children starting ART at 3 months or younger was twice as high in 2014–17 than in 2006–10. Most of these infants were in South Africa, where more than 80% of national uptake of both early infant diagnosis (including PCR HIV testing at birth) and universal treatment has been achieved. Previous observational studies have suggested increasing proportions of infants initiating treatment younger than 1 year.[6,7,12] Therefore, our findings might reflect slower uptake of early infant diagnosis and treatment, particularly in those regions in sub-Saharan Africa where HIV testing at birth is not done. For example, the proportion of HIV-exposed infants who received testing in their first 2 months of life in west and central Africa increased from 10·1% to 29·3% between 2010 and 2018, compared with an increase from 43·2% to 68·8% in east and southern Africa.[1]

We observed a modest decrease in the prevalence of advanced HIV disease markers (severe immunosuppression and underweight) at ART initiation. This trend is expected, because of expanded ART eligibility criteria for children and improved access to ART worldwide, but it remains concerning that about half of all children in the most recent calendar period were immunosuppressed, underweight, or had stunted growth at treatment initiation. Considering that age at ART initiation did not decrease significantly, this finding highlights the need for increased efforts towards early diagnosis and treatment before the onset of advanced disease. Expanding on previous findings on the high risk of mortality among infants younger than 12 months,[12,24] unadjusted estimates showed that infants starting ART aged 4–12 months had a higher risk of death compared with those aged 0–3 months, suggesting that older infants who might have been missed at earlier diagnosis could subsequently present to care when they are sicker and more likely to die. Our findings also show that even in 2014–17, a quarter of children still started ART with advanced disease. Unlike in adults,[1] the proportion of young children starting ART with advanced disease remains high. Intensifying early diagnosis and treatment efforts before the onset

	≤12 months (n=10 140)	13–36 months (n=14 504)	37–60 months (n=7575)
ART initiation year			
2006–2010	1	1	1
2011–2013	0·73 (0·62–0·87)	0·69 (0·58–0·82)	0·64 (0·46–0·89)
2014–2017	0·51 (0·40–0·65)	0·58 (0·46–0·73)	0·44 (0·27–0·71)
Country income group			
Low income	1	1	1
Lower-middle income	1·12 (0·89–1·42)	1·36 (1·11–1·66)	1·18 (0·80–1·73)
Upper-middle income	0·47 (0·38–0·59)	0·39 (0·30–0·51)	0·32 (0·18–0·57)
Region			
East Africa	1	1	1
West Africa	1·18 (0·86–1·61)	1·03 (0·78–1·37)	1·26 (0·79–2·00)
Central Africa	0·43 (0·17–1·05)	0·40 (0·21–0·74)	0·39 (0·15–0·98)
Southern Africa	0·69 (0·53–0·90)	0·78 (0·61–0·98)	0·56 (0·37–0·86)
Sex			
Male	1	1	1
Female	1·04 (0·90–1·20)	0·99 (0·85–1·15)	0·82 (0·62–1·07)
Severely immunosuppressed			
No	1	1	1
Yes	1·58 (1·31–1·91)	1·47 (1·14–1·90)	1·58 (1·01–2·48)
WAZ			
>–2	1	1	1
>–3 to ≤–2	1·76 (1·39–2·22)	1·76 (1·39–2·24)	1·60 (1·06–2·41)
≤–3	2·48 (2·10–2·92)	3·80 (3·17–4·55)	3·84 (2·78–5·30)

Data are adjusted hazard ratio (95% CI). Multivariable analysis was adjusted for sex, age at ART initiation , year of ART initiation, geographical region, country income group, immunosuppression status, and WAZ. Models were imputed for CD4% and WAZ. ART=antiretroviral therapy. WAZ=Weight-for-age Z score.

Table 3: **Mortality hazard ratios for children living with HIV in sub-Saharan Africa by age at ART initiation**

	10%	30%	50%	100%
Year of antiretroviral therapy start				
2006–09	1	1	1	1
2011–13	0·80 (0·72–0·88)	1·03 (0·95–1·10)	1·15 (1·08–1·23)	1·23 (1·18–1·30)
2014–17	0·65 (0·57–0·74)	0·80 (0·72–0·89)	0·87 (0·79–0·96)	0·99 (0·93–1·05)
Country income group				
Low income	1	1	1	1
Lower-middle income	1·29 (1·17–1·42)	1·32 (1·22–1·43)	1·32 (1·23–1·41)	1·31 (1·24–1·38)
Upper-middle income	0·60 (0·54–0·68)	0·62 (0·57–0·68)	0·63 (0·58–0·69)	0·64 (0·59–0·68)

Data are crude mortality hazard ratio (95% CI).

Table 4: **Mortality hazard ratios in various proportions of patients assumed to have died among participants lost to follow-up**

of advanced disease will ensure that the benefits of early diagnosis and treatment are achieved. Attention must be focused on this crucial group of children who might have fallen through the gaps in care because of late diagnosis, delayed turnaround of results, and poor engagement in care, all of which can be persistent in resource-limited settings. Programmes should aim to expand testing of infants to immunisation or outpatient clinics for infants whose mothers might have missed PMTCT. Furthermore, new perinatal transmissions and rapid disease progression in infants particularly in the era of widespread ART for prevention and treatment is associated with poor maternal health and wellbeing, and ART adherence issues in women who know their HIV status. Targeted care and support should be aimed at mothers and pregnant women into preventing transmission, promoting earlier diagnosis, and encouraging better follow-up of their infants.

Similar to previous studies, our results indicate decreasing 24-month mortality in children starting ART in sub-Saharan Africa since 2006 and across all country income groups, indicating a positive effect of implementation of universal ART.[25,26] Decreasing mortality was observed across all categories of age at ART initiation. Decreasing mortality need to be assessed alongside loss to follow-up, which is likely to include unascertained deaths, and varied across calendar periods. Nonetheless, the improved mortality persisted, unless we assumed that more than 50% of children lost to follow-up had actually died.

Overall, 1 in 5 of children was lost to follow-up, and loss to follow-up was high across all periods, peaking between 2010 and 2013. Young children living with HIV have been shown to be twice as likely as older children to be lost to follow-up, and children lost to follow-up are more likely than retained children to have advanced disease and greater immunosuppression, and not to be receiving ART.[27,28] High loss to follow-up among young children on ART remains a challenge in paediatric HIV care. Studies have shown a trend towards increasing loss to follow-up, with some studies attributing this to rapid programme expansion and patient decentralisation.[13,14,25,29] With the rapid scale-up of universal ART, pre-ART loss to follow-up could have shifted to loss to follow-up on ART, as children and their caregivers who had a high risk of not being retained in care, or who would have otherwise died before starting treatment, are being rapidly initiated on ART. Some caregiver characteristics have also been associated with loss to follow-up in children, including which caregiver is responsible, poor adherence, psychosocial factors such as stigma, and religious beliefs.[27,30] With a reduction in mother-to-child transmission of HIV and increasing scale-up of early infant diagnosis, children who acquire HIV despite these measures represent a group at high risk, and there is likely to be an increasing proportion of caregivers who have socioeconomic and psychosocial characteristics contributing to poor child outcomes. Hence, a growing need for a more holistic approach to care for children living with HIV exists, with particular attention to improving linkages to care and targeted tracing of caregivers to improve care engagement.

We found that children in lower-middle-income countries had a higher risk of mortality. Although in-depth analyses are needed to fully understand the reasons for higher mortality in lower-middle-income countries compared with low-income countries and upper-middle-income countries, they might be linked to numerous structural country-level and health system-level factors, donor funding, high prevalence risk factors for mortality such as malnutrition, and characteristics of the specific programmes that participate in IeDEA. Similarly, evidence from Lesotho,[1] a lower-middle-income country, suggests that mortality rate in children younger than 9 years living with HIV was 95 in 100 000 in 2018, the highest among all countries included in this study. Similar to comparisons of mortality by calendar period, mortality comparisons across country income groups in sub-Saharan Africa are challenging due to high and varying loss to follow-up. Nevertheless, across a range of assumptions about true mortality among children lost to follow-up, the disparity in mortality across country income groups persisted. As expected, low WAZ was also a strong predictor of mortality, with a higher risk observed among children older than 12 months at ART start compared with those 12 months or younger. This suggests that nutrition and poverty could accelerate HIV mortality differences in young children across country income groups.

This study has strengths and limitations. Because we included children living with HIV who initiated ART younger than 5 years, and considering that only 52% of children in sub-Saharan Africa who need ART are receiving it, we excluded an important group of children who were diagnosed younger than 5 years but were not linked to HIV care and ART initiation. South Africa was the only upper-middle-income country included, so our findings might not be generalisable to all upper-middle-income countries. Combining countries into income groups might not necessarily reflect how individual country practices and even individual cohort practices affect outcomes. Moreover, the number of cohorts included varies between countries, and country-level effects might not represent the country programme as a whole. As expected with routine data, approximately 25–40% of children had missing data on CD4% and anthropometry measures, for which we accounted by use of multiple imputation methods. We did sensitivity analyses using complete case data to check for possible bias introduced by imputing a large proportion of missing data. In addition, we had missing data on country-level information such as timing of uptake of universal ART guidelines, which could have influenced our findings. Finally, all-cause mortality was probably

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under-ascertained, and many deaths were probably miscategorised as lost to follow-up. However, our analyses considered this and recalculated mortality estimates under varying assumptions of mortality among those lost to follow-up. Despite these limitations, this study includes a very large sample of more than 32 000 children from across sub-Saharan Africa, allowing a population-level assessment of the effect of universal ART guidelines in children.

In conclusion, our findings highlight an improvement in the disease severity characteristics and mortality among children starting ART in large-scale ART programmes in resource-limited settings, but revealed persistent loss to follow-up and considerable heterogeneity across country income groups. There is still a need to increase focus on sustainable approaches for improved paediatric HIV programme uptake of early infant diagnosis, early ART initiation, and engagement and retention in care for young children living with HIV, particularly in low-income countries and lower-middle-income countries.

Contributors

VI, K-GT, and M-AD conceptualised and designed the study. VI analysed the data and wrote up the first draft of the manuscript. M-AD and K-GT accessed and verified underlying data. K-GT, MV, MY, RV, LA, SD, AE, MA-F, and M-AD provided extensive contribution into the manuscript. All authors reviewed and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

All data were linked and stored within IeDEA-southern Africa database at the regional Data Centre in the School of Public Health and Family Medicine, University of Cape Town, South Africa. Each site retains ownership of their original data. External users with a formal analysis plan can request access to the data through a formal process detailed on https://www.iedea.org/.

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Chapter 4: Earlier antiretroviral therapy initiation and decreasing mortality among HIV-infected infants initiating antiretroviral therapy within 3 months of age in South Africa, 2006-2017

Relevance of this paper to the thesis:

Following on from manuscript 1, this paper presents findings on the trends in paediatric ART outcomes with a specific focus on EID and treatment for infants starting antiretroviral therapy (ART) <3 months of age in South Africa. There is a high uptake of EID including birth PCR testing and early infant ART start, and a consequent increase in the number of infants starting treatment in South Africa, as observed from manuscript 1. Therefore, this chapter extends existing evidence on the benefits of early ART by describing the trends in characteristics at ART start, mortality and LTFU in a large cohort of early-treated infants over a 12-year period.

Contribution of the student and co-authors:

I conceptualized the analysis with technical advice from MD. I conducted all analyses and wrote the initial manuscript draft. All coauthors reviewed the manuscript and provided comments. All authors were involved with and approved the final draft of the manuscript

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Earlier Antiretroviral Therapy Initiation and Decreasing Mortality Among HIV-infected Infants Initiating Antiretroviral Therapy Within 3 Months of Age in South Africa, 2006–2017

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Background: Early infant diagnosis of HIV and antiretroviral therapy (ART) has been rapidly scaled-up. We aimed to examine the effect of expanded access to early ART on the characteristics and outcomes of infants initiating ART.

Methods: From 9 cohorts within the International epidemiologic Databases to Evaluate AIDS-Southern Africa collaboration, we included infants with HIV initiating ART ≤3 months of age between 2006 and 2017. We described ART initiation characteristics and the probability of mortality, loss to follow-up (LTFU) and transfer out after 6 months on ART and assessed factors associated with mortality and LTFU.

Results: A total of 1847 infants started ART at a median age of 60 days [interquartile range: 29–77] and CD4 percentage (%) of 27% (18%–38%). Across ART initiation calendar periods 2006–2009 to 2013–2017, ART initiation age decreased from 68 (53–81) to 45 days (7–71) (P < 0.001), median CD4% improved from 22% (15%–34%) to 32% (22–43) (P < 0.001) and the proportion with World Health Organization clinical disease stage 3 or 4 declined from 81.6% to 32.7% (P < 0.001). Overall, the 6-month mortality probability was 5.0% and LTFU was 20.4%. Mortality was 10.6% (95% confidence interval: 7.8%–14.4%) in 2006–2009 and 4.6% (3.1%–6.7%) in 2013–2017 (P < 0.001), with similar LTFU across calendar periods (P = 0.274). Pretreatment weight-for-age Z score <−2 was associated with higher mortality.

Conclusions: Infants with HIV are starting ART younger and healthier with associated declines in mortality. However, the risk of mortality remained undesirably high in recent years. Focused interventions are needed to optimize the benefits of earlier diagnosis and treatment.

Key Words: infants, early infant antiretroviral therapy, mortality, pediatric HIV, South Africa

(*Pediatr Infect Dis J* 2020;39:127–133)

In sub-Saharan Africa, an estimated 140,000 new HIV infections and 73,000 AIDS-related deaths occurred in 2018 among children 0–9 years of age.[1] Compared with older children, infants with HIV (HIV+) are prone to high early mortality and without antiretroviral therapy (ART), 50% will die before their second birthday.[2] Complexities related to testing, age and weight-related drug changes, rifampicin cotreatment of tuberculosis and limited drug formulations make infants a highly vulnerable population.

The World Health Organization's (WHO) guidelines for pediatric ART initiation have shifted from clinical and CD4-based criteria to immediate ART for all (Universal ART). In 2008, universal ART was recommended for all HIV+ infants <12 months of age based on findings from the Children with HIV Early antiRetroviral (CHER) trial.[3,4] In 2010, South Africa adopted universal ART for children <2 years of age. Furthermore, guidelines for lifelong universal ART for all pregnant and breast-feeding women living with HIV (so-called "Option B+")[5] and universal testing for HIV-exposed infants at birth were implemented in 2013 and 2015, respectively.[6] Consequently, by 2017, prevention of mother-to-child transmission of HIV (PMTCT) service uptake was >95%, the national coverage of early infant diagnosis (EID) and birth HIV testing uptake were both >90% and pediatric ART coverage was >75%.[1,7]

With expanded ART access, the demographic and clinical characteristics of recently infected infants may differ from those infected before the introduction of Option B+ and early testing. For example, prematurity, low birth weight, immunosuppression and comorbidities may be more prevalent in those becoming HIV-infected despite widespread coverage of Option B+. Of note, infants with these "high risk" characteristics were excluded from the CHER trial; therefore, the survival benefit may not be generalizable to current programmatic settings, especially in resource-limited settings where infants still present for treatment with advanced HIV disease.[8–10] While the outcomes of infants infected before the availability of EID and early ART have been described,[10–13] there are limited data on infants initiating early ART before 3 months of

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age outside research-controlled settings, in the context of improved EID practices and widespread access to ART. Using observational data, we examined temporal trends in the characteristics and outcomes of HIV+ infants.

MATERIALS AND METHODS

Study Setting and Participants

We conducted a retrospective cohort study using data from 9 International epidemiology Databases to Evaulate AIDS-Southern Africa (IeDEA-SA) cohorts in South Africa. IeDEA is a global research consortium which collects routine anonymized data on patients receiving HIV care and treatment.[14] Eight of the 9 sites included are mostly in urban areas representing primary, secondary and tertiary levels, while 1 site represents a private health sector facility. All sites contributing data to this study have relevant institutional and ethical approval.

We included ART-naïve infants (except for exposure to PMTCT drugs), initiating ART ≤3 months of age from January 2006 (first WHO treatment guidelines for children) to November 2017. To better understand the effect of changing WHO eligibility criteria for ART initiation and expansion of PMTCT programs between 2006 and 2017, infants were grouped according to the calendar year of ART initiation: 2006–2009, 2010–2012 and 2013–2017 representing the implementation of WHO ART eligibility for all HIV-infected children <2 years in 2010 and Option B+ in 2013, respectively. The entry point for this study was the earliest date of ART initiation at the IeDEA-SA clinical site. We defined ART as a combination of ≥3 antiretroviral drugs from ≥2 different drug classes. The recommended first-line regimen for children <3 years of age before 2010 was stavudine, lamivudine and lopinavir/ritonavir. From 2010, national treatment guidelines recommended that abacavir replace stavudine in the first-line regimen. Guidelines also recommend that newborns receive zidovudine, lamivudine and nevirapine for the first month or until >3 kg.

Outcomes and Key Variable Definitions

Our primary analysis described ART initiation characteristics and outcomes of mortality, loss to follow-up (LTFU) and transfer out (TFO) to other facilities by 6 months on ART, compared across calendar periods. We also described weight-for-age Z score (WAZ) improvement in those retained for 6 months after ART initiation. Mortality included all-cause mortality and LTFU was defined as not having any documented clinic visit or laboratory result within a window period of 4–9 months after ART initiation, irrespective of whether the child returned to care >9 months after ART initiation. We further distinguished infants with no visits after the date of ART initiation for up to 9 months as having "no follow-up" while those with ≥1 subsequent visit within the first 3 months on ART but with no visit between 4 and 9 months after ART initiation were classified as "LTFU but with subsequent follow-up on ART."[15] WAZ improvement by 6 months on ART was assessed using the measure closest to 6 months (window 4–9 months). Analysis of outcomes was limited to infants starting ART ≥6 months before database closure. Follow-up was right-censored at the earliest of death, last clinic visit (for patients LTFU), date of TFO or 6 months after ART start.

WAZ was calculated using the WHO Child Growth Reference Standards.[16] We defined underweight as WAZ ≤−2 and severely underweight as WAZ ≤−3. Immunosuppression was classified using CD4% as severe (<15), moderate (15%–24%) or absent (>25%).[17] When describing weight measurements and laboratory values at ART initiation, we selected the measurement closest to ART start date within a window of −3 weeks to +1 month for WAZ and −6 months to +2 weeks after ART start for viral load, CD4 counts and percentages.

Statistical Analysis

We compared ART initiation characteristics across calendar periods using the χ^2 or Fisher exact test (in the case of sparse data) and Kruskal-Wallis test for categorical and continuous variables, respectively. We used Kaplan-Meier methods to estimate the probability of mortality, LTFU and TFO and compared survival using the log-rank test. Due to the interdependence of mortality, LTFU and TFO, we also conducted competing risks analysis to calculate the cumulative incidence functions for these outcomes.

We used Cox regression to determine ART initiation characteristics associated with mortality and LTFU. Patient-level covariates included in the models were selected a priori as potential confounders based on their clinical relevance and data availability and included age, sex, clinical stage, WAZ <−2, $\log_{10}$ viral load, CD4 percentage or immunosuppression level, WHO disease stage, PMTCT exposure, year of ART initiation (2006–2009, 2010–2012 and >2013). Adjusted Cox regression models were stratified by clinical site to account for heterogeneity.

We addressed missing baseline data for WAZ, viral load, WHO disease stage and CD4 cell counts and percentages using multiple imputation methods. The imputation model relied on the assumption of data missing at random and included all ART initiation characteristics, cohort, year of ART initiation and outcome variables. We generated 10 imputed dataset and combined estimates using Rubin Rules.[18] We performed a sensitivity analysis to assess predictors of mortality including only patients with complete case data. All statistical analyses were completed using STATA 15.0 (STATA Corporation, College Station, TX).

RESULTS

ART Initiation Characteristics

Between 2006 and 2017, 17,854 HIV+ children <5 years old initiated ART in the IeDEA-SA sites in South Africa (Fig. 1). Among these, the proportion starting ART ≤3 months of age increased from 6.3% to 20.5% in 2006–2009 and 2013–2017, respectively ($P < 0.001$). The median age was 60 days [interquartile range (IQR): 29–77] and differed substantially by calendar period, ranging from 68 days in 2006–2009 to 45 days in 2013–2017 ($P < 0.001$). There was a marked increase in the proportion of infants starting treatment within 1 month of age; 7% in 2006–2009, 14% in 2010–2012 and 44% in 2013–2017. The median CD4% was 27%, improving from 22% in 2006–2009 to 32% in 2013–2017 ($P < 0.001$). There was a pattern toward an increase in the proportion of females and median log viral load over time. Half of all infants were classified with WHO disease stage 3 or 4, however, this proportion decreased substantially over time; 81.6% in 2006–2009 vs. 32.7% in 2013–2017, $P < 0.001$ (Table 1). Compared with infants starting ART in the first month of age (0–30 days), those starting between 31 and 60 days and 61 and 90 days of age were more likely to be underweight (WAZ <−2) (38.5% vs. 60.6% and 60.1%; $P < 0.001$).

Programmatic Outcomes

Among 1692 infants, 86 (5.0%) died, 353 (20.8%) became LTFU and 144 (10.2%) were TFO. The 6-month cumulative probabilities of mortality [95% confidence interval (CI)], LTFU and TFO were 6.4% (5.2–7.9), 21.5% (19.4–23.3) and 10.6% (9.0–12.3), respectively. Mortality probability was highest among infants initiating ART in 2006–2009 [10.6% (7.8–14.3)] compared with 2013–2017 [4.6% (3.1–6.7)] (log-rank test $P < 0.001$). LTFU remained similar across calendar period, ranging from 23.8% (20.2–28.0) in 2006–2009 to 21.0% (18.1–24.3) in 2013–2017 (log-rank test $P = 0.2746$). Competing risk analysis yielded similar estimates

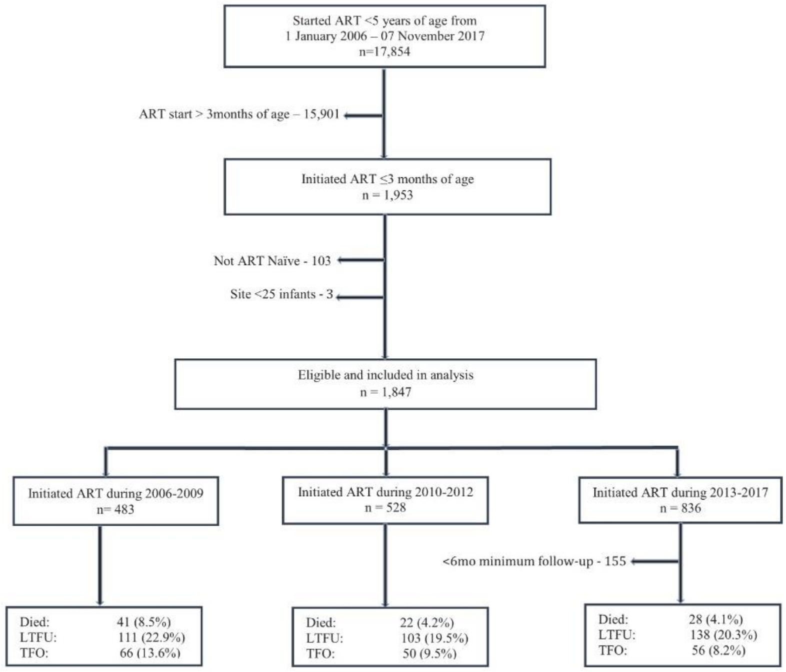

FIGURE 1. Flow chart describing participant selection and outcomes of infants with HIV initiating ART ≤3 months of age from 2006 to 2017 in South Africa.

as shown in Figure 2 and Table 1, Supplemental Digital Content, http://links.lww.com/INF/D695.

The median follow-up time for infants who died was 33 (21–88), for LTFU was 0 (0–18) days and for TFO was 45 days (12–94) days. For the 2006–2009 period, death occurred at a median of 27 days (15–57) versus 45 days (21–85) in the latest period. The median age at death was 94 days (IQR: 79–134), with no significant difference across ART initiation time periods ($P = 0.4655$). In addition, 61.5% of infants who died initiated treatment between 61 and 91 days of age. Among those LTFU, 74% did not return for a clinic visit after the date of ART initiation for up to 9 months, while 26% returned for a subsequent visit after initiating ART (within 3 months on ART) and thereafter were LTFU from 3 to 9 months after ART initiation.

Risk Factors for Mortality and LTFU

Relative to ART start between 2006 and 2009, the unadjusted mortality hazard ratio (uHR) was lower for infants starting ART in 2010–2012 and 2013–2017 (Table 2); however, this effect was attenuated after adjusting for disease severity at ART start. Compared with having WAZ >–2, infants with WAZ ≤–2 had a 1.7-fold [adjusted HR (aHR), 1.74; 95% CI: 1.07–2.81] increased risk of death (Table 2).

We observed a decreasing risk of LTFU (ie, no follow-up and LTFU but with subsequent follow-up on ART) over time. Initiating ART between 2010–2012 and after 2013 were associated with a decreased unadjusted hazard of LTFU (aHR 0.54, 95% CI: 0.40–0.73 and aHR: 0.46, 95% CI: 0.33–0.62, respectively), compared with 2006–2009. Infants with unknown maternal or infant PMTCT status at ART initiation had a 2.4-fold increased risk of being LTFU immediately after the date of ART initiation (no follow-up) (aHR: 2.43, 95% CI: 1.32–4.59). None of the infant ART initiation characteristics included was associated with LTFU after at least 1 subsequent visit after ART initiation (Table 2, Supplemental Digital Content, http://links.lww.com/INF/D695). Overall, we obtained similar estimates when complete case analysis was conducted, except for no decrease in risk of LTFU in the most recent calendar period (Table 3, Supplemental Digital Content, http://links.lww.com/INF/D695).

Weight Improvement

At ART initiation, the median WAZ (IQR) at initiation was –2.4 (–3.7 to –1.1), varying significantly across calendar periods ($P < 0.001$), 56% of all infants had WAZ ≤–2 (underweight = 19.3% plus severely underweight = 34.8%). After 6 months on ART, the median WAZ was –1.19 (–2.3 to –0.3) which did not differ by calendar period of ART initiation ($P = 0.949$); 30% of infants had WAZ ≤–2.

DISCUSSION

In this study of infants with HIV starting ART ≤3 months of age, we found that an increasing proportion of infants started ART at younger ages and with less advanced HIV disease. Overall, mortality was 5.0% with marked differences between the calendar periods. Although mortality was halved from 2010 onward, mortality remained at 4.1% after 2013. An unchanging proportion of 1 in 5 infants were LTFU after 6 months of ART, with nearly 3 quarters of those having no follow-up after their ART initiation visit. Declining mortality is possibly mediated by earlier ART initiation reflecting the real-world benefit of the shift to universal ART for infants and simultaneous expansion of EID access, particularly birth testing in South Africa.

Characteristics of infants starting ART improved across calendar periods. A marked increase in the proportion of infants ≤1 month of age at initiation was a major driver of decreasing age at

TABLE 1. Characteristics of Infants Who Initiated Antiretroviral Therapy at ≤3 mo of Age Across South Africa

Characteristics	Overall N = 1847	2006–2009 N = 483	2010–2012 N = 528	2013–2017 N = 836	*P
Age at ART start (d)	60 (29–77)	68 (53–81)	67 (46–80)	45 (7–71)	<0.001
Age category (d)					
0–30	479 (25.9)	34 (7.0)	77 (14.5)	368 (44.0)	<0.001
31–60	464 (25.1)	155 (32.1)	141 (26.7)	168 (20.1)	
60–90	905 (48.9)	294 (60.8)	310 (58.7)	300 (35.8)	
Female	1028 (55.6)	250 (51.8)	317 (60.0)	461 (55.1)	<0.031
CD4 count (cells/μL)	1073 (407–1955)	899 (396–1718)	1274 (487–2028)	1149 (350–2070)	<0.035
CD4 percentage	27 (18–38)	22 (15–33)	26.2 (18–36)	32 (22–43)	<0.001
CD4% for age <30 days	42 (27–51)	21 (16–28)	38.6 (24–51)	44.3 (31–52)	0.005
CD4% for 31–60 days	27 (19–39)	26 (18–38)	26 (16–40)	32 (23–40)	0.053
CD4% for 61–90 days	24 (16–33)	21 (14–31)	24 (18–33)	26 (16–33)	<0.001
Missing, N (%)	817 (44)	156 (32)	188 (35)	473 (56)	
Immunosuppression					
>25% (none)	556 (54)	143 (43)	177 (51.9)	246 (67.6)	<0.001
>15 to ≤25% (moderate)	284 (27)	104 (31)	110 (32.3)	70 (19.2)	
≤15% (severe)	182 (17)	80 (24)	54 (15.8)	48 (13.2)	
Missing, N (%)	817 (44)	156 (32)	188 (35.6)	473 (56.5)	
Log_{10} viral load	5.8 (4–6)	5.0 (5–6)	6.0 (5.0–6.6)	5.3 (3.8–6.3)	<0.001
Viral load (copies/mL)					
<100,000	253 (27.4)	47 (15.4)	63 (22.8)	143 (41.7)	<0.001
>100,000–1 million	282 (30.5)	125 (40.9)	72 (26.1)	85 (24.7)	
>1 million	389 (42.1)	133 (43.6)	141 (51.1)	115 (33.5)	
Missing, N (%)	923 (44.9)	178 (36.8)	252 (47.7)	493 (58.9)	
WHO clinical stage					
I/II	592 (47.6)	65 (18.4)	152 (45.7)	375 (67.3)	<0.001
III/IV	652 (52.5)	289 (81.6)	181 (54.6)	182 (32.7)	
Missing, N (%)	604 (32.7)	129 (26.7)	196 (37.1)	279 (33.3)	
WAZ	−2.4 (−3.7 to −1.1)	−2.9 (−4.2 to −1.7)	−2.3 (−3.6 to −1.0)	−1.7 (−3.2 to −0.5)	<0.001
WAZ category					
<−3	316 (34.8)	146 (43.7)	94 (32.6)	76 (26.6)	<0.001
−3 to −2	175 (19.3)	70 (21.1)	62 (21.5)	43 (15.0)	
>−2	418 (45.9)	118 (35.3)	132 (45.8)	167 (58.3)	
Missing, N (%)	940 (50.9)	149 (30.8)	241 (45.6)	550 (65.7)	
†PMTCT exposure					
No	952 (51.5)	197 (40.8)	250 (47.3)	505 (60.4)	<0.001
Yes	233 (12.6)	43 (8.9)	38 (7.2)	152 (18.2)	
Unknown	662 (35.8)	243 (50.3)	240 (45.5)	179 (21.4)	

*P values were derived from χ^2 and Kruskal-Wallis tests, where appropriate. Values are given as number (%) or median (interquartile range).
†Maternal or infant PMTCT exposure.

ART start. We attribute this finding to improved EID services and the resulting high coverage of >90% in South Africa after the introduction of universal birth testing in 2015. However, considering the recent context of expanded EID and treatment programs, infants infected after 2013 still started ART relatively late at a median age of 45 days. Similar to previous findings, we found that infant immune status at ART start improved over time.[10,12]

Infants acquiring HIV despite the availability of PMTCT are more likely to be those missed by PMTCT programs, who present for testing when they become sick rather than through routine infant follow-up.[19] For example, infants initiating ART between 61 and 90 days old were more likely to be underweight than those initiating before 30 days old (57% vs. 38%) and underweight infants were more likely to die.[10,20] This suggests that older infants are those who missed earlier testing or were infected during the early postpartum period and only present to care with advanced disease and hence higher risk of mortality. This partially explains the ongoing burden of advanced disease despite high birth testing coverage among those known to the PMTCT program. The national expansion of PMTCT (>95%) was reflected in our study as the proportion of infected infants with PMTCT exposure doubled in the latest cohort. Compared with the era of limited access to PMTCT, recent peri- and postnatal transmissions may be occurring among an emerging vulnerable population of mothers. These women may have either not engaged with the health system or were not virally suppressed despite accessing care due to complex social and medical challenges that influence health-seeking behavior and ART adherence.

Previous ART implementation studies in infants before the expansion of early diagnosis and ART for prevention and treatment suggests a trend toward decreasing longer-term mortality over time.[10,21,22] Our findings extend existing evidence to include trends in short-term mortality in early-treated HIV+ infants. The effect of lower mortality over time was not retained after adjusting for disease severity, suggesting that mortality reduction was mediated by earlier ART initiation and improved infant characteristics. The probability of survival for period 2013–2017 was 93%, lower than the estimated 6-month survival probability of 97% for the general population of South African infants.[23] The true mortality difference between children with and without HIV is likely even greater due to the inherent survival bias due to infant follow-up from ART start in our cohort. An estimated 12-month mortality of 14% has been reported in a recent cohort of birth-identified HIV+ infants, suggesting significant mortality despite ART in this cohort.[24]

The CHER trial enrolled infants starting ART <12 weeks of age (excluding infants with a birth weight <2 kg, advanced HIV and CD4 depletion) and followed up for a median of 40 weeks comparing early and deferred ART.[4] Mortality in our population during the 2013–2017 period was 4.6%, compared with 4.0% reported in the CHER trial arm for immediate ART. Although higher mortality rates would be expected in our population, a

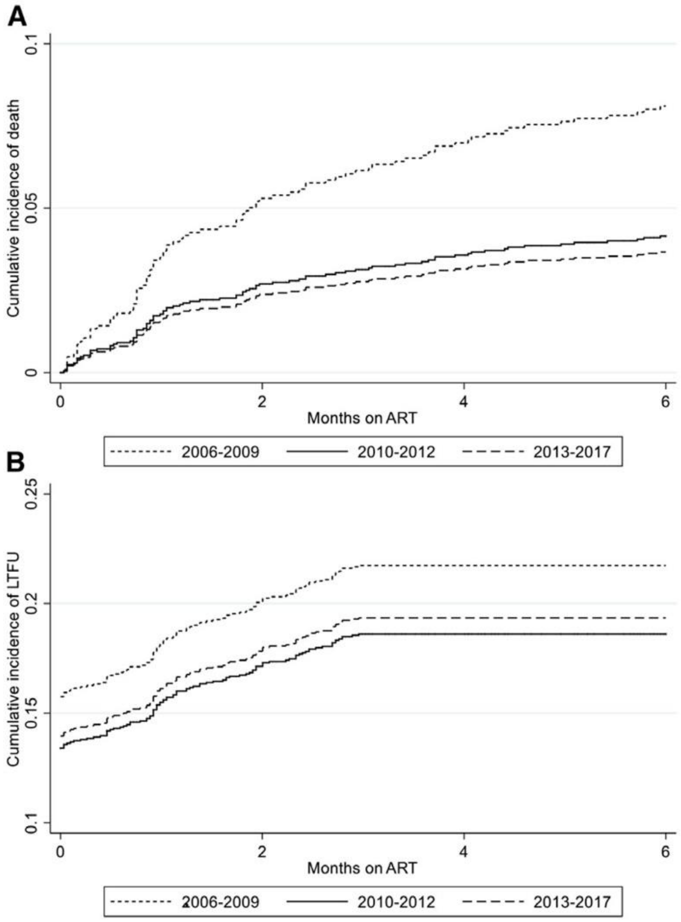

FIGURE 2. Cumulative incidence functions stratified by calendar period of ART initiation for: (A) mortality accounting for LTFU and TFO as competing events, (B) LTFU accounting for death and TFO as competing events. Plot shows time to LTFU defined as no visit from 4 to 9 months on treatment.

shorter follow-up period and high LTFU may have masked true mortality. While it is concerning that mortality did not decline further during the latest period (compared with 2010–2012) when both Option B+ and birth EID were implemented, characteristics such as prematurity and associated complications, and infectious comorbidities may have contributed to poorer outcomes. Furthermore, because we only measured mortality after ART start, it is possible that infants who previously would have died before being diagnosed and/or starting ART are now initiating ART earlier, and that pre-ART mortality has shifted to mortality after early ART initiation. These explanations are supported by another study which reported that 15% more HIV+ infants were lost from the ART program by 1 year among those who started after 2012 relative to those starting before 2010.[25]

More than half of deaths occurred in the first 3 months of ART initiation and mostly in the 2006–2009 cohort, similar to earlier studies.[26] While high rates of bacteremia and immune reconstitution inflammatory syndrome have been associated with high early mortality, earlier ART start with higher CD4 percentages has likely resulted in immune reconstitution inflammatory syndrome becoming less common.[27]

The high proportion of infants with no follow-up is particularly concerning. Increased mobility and poor HIV service retention soon after delivery among women living with HIV are well documented and contribute to low retention of infants soon after initiating treatment.[28] While poor documentation of transfer between health care facilities may underestimate retention, high early LTFU may contribute to mortality under-ascertainment. In this respect, although overall LTFU did not decrease over time, the risk of LTFU after adjustment for disease severity reduced in recent years suggesting that true LTFU may be reduced. Improved focus on retention and shift toward individualized care may be more feasible in the context of a decreased overall burden of pediatric HIV. As with mortality, it is possible that that pre-ART LTFU has been shifted to LTFU on ART after the implementation of birth diagnosis and universal ART.

To our knowledge, this is the largest study of early infant ART outcomes in sub-Saharan Africa. This study includes data from routine care cohorts representing different levels of health care in South Africa. In addition, the study period covers several guideline periods, allowing assessment of the influence of guideline changes while reflecting the realities of routine, resource-limited settings.

The routine nature of the settings from which data were collected is evident from the amount of missing data. Lack of data on PMTCT, maternal socioeconomic factors and comorbidities such as tuberculosis may have led to residual confounding. We found an increased risk of death among underweight infants but could

TABLE 2. Cox Proportional Hazards Model of Imputed Dataset Stratified by Cohort: Infant Characteristics Associated With Mortality and Loss to Follow-up in the First 6 months on ART (n = 1692)

	Mortality		Loss to Follow-up	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age in weeks	1.47 (0.89–2.45)	0.95 (0.53–1.71)	0.93 (0.74–1.17)	0.89 (0.68–1.15)
Female	0.68 (0.44–1.02)	0.70 (0.46–1.07)	0.89 (0.72–1.09)	0.88 (0.71–1.09)
ART initiation year				
2006–2009	Ref		Ref	
2010–2012	0.47 (0.27–0.79)	0.76 (0.42–1.36)	0.77 (0.59–1.01)	0.54 (0.40–0.73)
2013–2017	0.46 (0.28–0.75)	0.98 (0.54–1.75)	0.80 (0.62–1.03)	0.46 (0.33–0.62)
WHO disease stage				
I/II	Ref		Ref	
III/IV	1.85 (1.14–2.99)	1.08 (0.61–1.91)	0.87 (0.65–1.14)	0.91 (0.65–1.28)
CD4 percentage	0.98 (0.96–0.99)	0.98 (0.96–1.00)	0.99 (0.98–1.00)	1.00 (0.99–1.01)
WAZ				
>−2	Ref		Ref	
≤−2	2.43 (1.53–3.84)	1.74 (1.07–2.81)	0.93 (0.70–1.23)	0.95 (0.71–1.26)
Log viral load	1.38 (1.07–1.58)	1.14 (0.89–1.46)	0.97 (0.88–1.08)	1.02 (0.92–1.13)
*PMTCT exposure				
No	Ref		Ref	
Yes	1.17 (0.74–1.85)	0.87 (0.50–1.49)	0.59 (0.46–0.77)	1.05 (0.61–1.69)
Unknown	1.10 (0.62–1.97)	1.20 (0.50–2.86)	0.83 (0.62–1.11)	1.08 (0.65–1.78)

*Status of infant exposure to maternal or infant PMTCT.

not assess the extent to which prematurity and low birthweight are responsible because of limited data on gestational age and weight at birth. There is a chance of survival bias in our selected cohort may have led to an under-estimation of mortality.

CONCLUSIONS

There have been improvements in the characteristics of infants starting ART and an associated decline in mortality over time. Nevertheless, early death and LTFU remain unacceptably high. Considering the risk of mortality did not decrease further after 2010, there is a need to better understand the specific health-care needs of this population of infants who continue to acquire HIV despite widespread PMTCT and ART access and uptake.

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Chapter 5: Virologic and immunologic responses to first-line antiretroviral therapy initiated during early infancy in South Africa

Relevance of this paper to the thesis:

This manuscript addresses a viral suppression, a key measure of ART effectiveness. It assesses the trends in the rates of short-term viral suppression among early-treated infants over time and examines the predictors of non-suppression. Achieving viral suppression among infants is challenging, however there are few studies that show how expansion in PMTCT and ART over time may be related to trends and variations in viral suppression. This chapter therefore assesses viral suppression among several paediatric cohorts while using the lowest common denominator viral suppression threshold (<400 copies/ml) which improves on the significant disparity in viral suppression thresholds reported.

Contribution of the student and co-authors:

I conceptualized the design of the study with support from MD and KT. I conducted the analyses and drafted the manuscript. All coauthors reviewed the manuscript and provided conceptual input. All authors reviewed and approved the final manuscript draft

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Virologic and immunologic responses to first-line antiretroviral therapy initiated during early infancy in South Africa

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Abstract

Introduction: The responses of HIV-positive infants to universal antiretroviral therapy (ART) are poorly understood, especially in the context of widespread effective HIV vertical transmission prevention (VTP) and early infant diagnosis. We described the temporal trends in virologic and immunologic responses among HIV-positive infants enrolled within 9 International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) South African sites.

Methods: Infants who initiated ART <3 months of age between 2006-2016 were studied. We examined viral suppression (viral load [VL] <400 copies/ml) and immunologic response up to 12 months on ART according to the calendar period of ART initiation: 2006–2009, 2010-2012, and 2013-2016. We used logistic regression models to examine factors associated with unsuppressed VL (>400 copies/ml) by 6 and 12 months on ART.

Results: Among 809 infants, median (IQR) age and VL at ART initiation were 53 (24-71) days and 5.8 (4.8-6.4) $\log_{10}$ copies/ml respectively. By 6 and 12 months on ART, 56% and 65% infants achieved virologic suppression and the median (IQR) CD4 percentages increased slightly to 30% (22-37) and 31% (25-39) respectively, from a median of 27% (18-38) at ART initiation. Fewer infants (52% at 6 months; 60% at 12 months) achieved virologic suppression in 2013-2016 than in 2006-2009 (63% at 6 months; 72% at 12 months), p=0.030 and p<0.001. Pre-treatment VL >1 million copies/ml ([aOR]:2.35, 95% CI: 1.32-4.20) and CD4% <25% (aOR: 1.47, 95% CI: 0.99-2.28) were associated with having a VL >400 copies/ml at 6 months on treatment.

Conclusions: We observed poorer viral suppression levels among infants initiating early ART in recent calendar years, despite improvement in CD4% and lower VL at ART initiation. These findings highlight the persistent suboptimal outcomes of infants with HIV in the era of birth diagnosis and early infant ART.

Introduction

Several studies have shown that early antiretroviral therapy (ART) in infants considerably reduces morbidity and mortality in infants with HIV infection [1-4]. Therefore, the World Health Organization guidelines have changed accordingly to recommend early infant diagnosis including birth testing and universal ART for all children regardless of clinical or immunological status since 2013 [5-7]. With evolving guidelines and intensified efforts to achieve the UNAIDS 90-90-90 policy target, uptake of paediatric ART has increased and occurs at progressively younger ages. However, achieving viral suppression in 90% of all people living with HIV on ART is especially challenging in infants.

Infants commonly present with considerably higher viral loads (VL) at ART initiation and are less likely to fully supress than older children [8-10]. In a metanalysis of paediatric studies from low- and middle-income countries, among children started on ART between 2009-2011, 72.7% (95% CI 62.6 to 82.8) achieved VS within 12 months [11]. A previous study from Southern Africa showed that only 28% and 56% of infants commencing ART before 12 months of age achieved virologic suppression below <400 copies/ml after 6 and 12 months of therapy [12].

Achieving viral suppression in infants on ART is challenging for various reasons. Certain clinical and social factors such as advanced HIV disease [13], malnutrition, co-morbidities, pre-treatment HIV drug resistance due to prior exposure to drugs as part of vertical transmission prevention (VTP) interventions and prematurity may be more frequent among recently infected infants in resource-limited settings and may hamper optimal responses to early ART. In addition, variability in children’s weight, limited drug options and poor palatability of widely used formulations may lead to a greater number of infants not achieving virologic suppression and developing antiretroviral resistance [14-16].

Little is known about the virologic and immunologic responses of infants with HIV enrolled in routine HIV care settings, in the context of early infant ART and increased access to effective VTP programmes. In addition, there is significant disparity in viral suppression thresholds in published reports [17-19]. Therefore, using data from International epidemiology Databases to Evaluate AIDS – Southern Africa (IeDEA-SA) we investigated virologic and immunologic response to early ART initiated before three months of age and assessed the predictors of viral non-suppression among infants starting early ART in a large paediatric cohort.

Methods

Study population and design

We analysed data collected prospectively from infants in nine South African cohorts contributing IeDEA-Southern Africa (IeDEA-SA) from 2006-2016. IeDEA is a multi-regional HIV cohort collaboration, which has been previously described [20]. Cohorts included represent routine HIV care facilities across primary (Gugulethu, Khayelithsha, Hlabisa, Kheth'Impilo), secondary and tertiary (Red Cross War Memorial Children's Hospital, Tygerberg Children's Hospital, Harriet Shezi Children's Clinic at Chris Hani Baragwanath academic Hospital and Rahima Moosa Mother and Child Hospital) levels of care, with one cohort (Aid for AIDS) representing the private care sector.

Ethics

All participating sites have institutional ethical approval from the relevant Institutional Review Boards (IRBs) to contribute anonymized individual patient data to the IeDEA-SA Data Centres. Most local IRBs waived the need for informed consent for analysis of de-identified routine patient data, but where the IRB required informed consent, this was obtained from the caregiver. IeDEA-SA data are collated at clinical sites by cohort investigators at routine clinical follow-up of infants as part of the standard of care. Anonymized data are then transferred to the central IeDEA-SA Data Centre using a standard Data Transfer Protocol.

Outcomes and key definitions

We included HIV-positive infants within IeDEA-SA databases if they were ART naïve and initiated first-line combination ART ≤12 weeks of age and had at least one VL measure at 6 months after ART initiation. The study population was categorized according to calendar year of ART initiation corresponding to changes in PMTCT and infant treatment eligibility guidelines: 2006-2009, 2010-2012 and 2013-16. In South Africa the Option A prevention of MTCT (PMTCT) approach was introduced in 2008 and was revised in 2010, followed by implementation of Option B in 2013 and Option B+ in 2015. South African National Guidelines also recommended immediate treatment for all infants less than 12 months of age regardless of clinical or immunologic status in 2010 [21]. This recommendation was subsequently extended to include all children less than 5 years of age in 2013 [22]. Combination ART was defined as three or more antiretrovirals from at least two drug classes in a single regimen following at least one positive infant HIV-PCR test. In South Africa, the first-line regimen recommended for children

<3 years old before 2010 was stavudine, lamivudine and lopinavir-ritonavir. By 2010, abacavir replaced stavudine in the first-line ART regimen. In 2015, the national treatment guidelines recommended that new-born infants living with HIV be treated with zidovudine, lamivudine and nevirapine for the first month or until reaching 3kg body weight. Thereafter, abacavir and lopinavir-ritonavir should replace zidovudine and nevirapine respectively. Viral load monitoring is recommended at 6 and 12 months after ART start and 12-monthly thereafter provided that the VL remains suppressed.

The primary outcome was virologic suppression (HIV RNA level <400 copies/ml) by six months on ART. We also assessed the viral suppression at 12 months among a subset of infants who had additional VL measures between 9-15 months on ART. The secondary outcome was immune recovery by 6 months on ART. Median CD4 percentages at ART initiation and 6 months were compared.

ART initiation characteristics included age at ART start, VL, CD4 count and percentage, WHO clinical disease stage, calendar year of ART initiation, WAZ, PMTCT exposure status and initiating ART regimen. WAZ was calculated using the WHO Child Growth standard [23] and included measurements taken from 1 month before to 2 weeks after ART initiation. CD4 and VL values measured between 1 month before and 2 weeks after ART initiation were considered as ART initiation measures. For six and twelve month outcomes, we used VL and CD4 count and percentage measures taken within a window of 4-9 and 9-15 months after ART start respectively. In instances where multiple values were available per time frame, the date closest to the ART start date and estimated six and twelve months visit dates were used for ART initiation and follow-up measures respectively.

Statistical analysis

We described ART initiation and follow-up characteristics using proportions, medians with inter-quartile ranges (IQR), and means with standard deviations (SD). We used chi-squared tests to compare proportions of infants virologically suppressed across calendar periods. We also compared the mean CD4 percentage at 6 months across calendar ART initiation cohorts using the Kruskal-Wallis test.

We used multivariable logistic regression models to identify ART initiation characteristics associated with viral non-suppression (VL >400 copies/ml) by 6 months on ART. The multivariable logistic regression model was adjusted *a priori* for age at ART initiation, sex, WAZ (WAZ <-2 and >-2), CD4 percentage, VL (<100,000, 100,000-1 million and >1 million copies/ml), year of ART initiation and for intra-site clustering across the nine facilities. To account for missing data for key characteristics at ART start including CD4 counts and percentage, WAZ, viral load and WHO stage, we performed multiple imputation under the assumption of data missing at random (MAR), generating 10 imputation sets due to moderately high levels of missing data. The imputed models included all key ART initiation variables and the outcome variable of VL at six months was included to inform missingness. Data management and analysis were performed using STATA statistical software (Release 15, StataCorp LP, College Station, TX).

All participating sites have institutional ethical approval from their respective institutional review boards to contribute data to IeDEA-SA analyses. The Universities of Cape Town and Bern have institutional ethical approval to conduct analyses on the anonymized merged data.

Results

Characteristics at ART start

Of the 1847 infants who initiated ART <3 months of age between 2006-2016, we included 809 (43.8%) infants with at least one viral load measure by 6 months on ART (Figure 1). Table 1 shows the characteristics of infants at ART start stratified by calendar period of ART initiation. At treatment initiation, the median (IQR) age and log10 VL (IQR) was 53 (24-71) days and 5.8 (4.8-6.4) copies/ml respectively. Infants starting ART after 2013 had significantly lower median age and viral loads, and higher CD4 percentages at ART start compared to those starting between 2006-2012. Availability of VL measures at ART initiation progressively decreased over time (76% in 2006-2009 and 68% in 2010-2012 versus 60% in 2013-2016). The proportion of infants with VL >1 million copies/mL at ART start was lower in the later period than the early and intermediate periods (32% in 2006-2009 versus 21% in 2013-2016, $p<0.001$). In addition, the distribution of infant regimen across infants in the different calendar periods reflect the changes in regimen guidelines, with the abacavir-based regimen becoming the predominant first-line regimen among infants initiating ART after 2010 (Table 1).

Virologic and immunologic outcomes

Overall, 56% and 65% infants attained virologic suppression by 6 and 12 months on ART, respectively. The median (IQR) $\log_{10}$ VL by 6 and 12 months after commencing ART was 2.6

(2.09-3.92) and 2.5 (1.9-3.3) respectively. Viral suppression levels across individual cohorts at both timepoints ranged from 30.5% to 66.2% and from 59.2% to 67.2% respectively. There was a trend towards worsening viral suppression levels with increasing calendar year of ART initiation, from 63% for those initiating ART in 2006-2009, to 52% in 2013-2016 by 6 months on ART (p=0.030). Similarly, by 12 months on ART, 76% achieved viral suppression in 2006-2009 which decreased to 60% in 2013-2016 (p<0.01) (Figure 2). Furthermore, a total of 116 (14%) infants overall did not achieve virologic suppression at both 6 and 12 months on ART. Infants in this category had a median (IQR) age and CD4% at ART initiation of 9.5 (6.1-12) and 24.8 (18.3-36.4); about half of them had a baseline viral load of >1 million copies/ml, were exposed to maternal or infant PMTCT regimens and had signs of advanced clinical disease (Table S1).

The median (IQR) CD4 percentages overall by 6 and 12 months on ART were 30% (22-37) and 31% (25-39) respectively. There were no significant differences in median CD4 percentages at 6 and 12 months on ART across calendar periods (p=0.161 and p=0.266 respectively) (Figure 3).

In stratified analysis, infants who did not achieve viral suppression by 6 months on ART were more likely to be older (55 (32-73)50 (16-68) and have higher viral loads at ART initiation 6.0 (5.3-6.4) vs5.7 (4.5-6.3) (Table S2).

Univariate logistic models showed that ART start characteristics including older age, later year of ART initiation (>2010), higher viral load, WHO disease stage 3 or 4 and starting regimen were associated with unsuppressed VL by 6 months on ART. While later year of ART initiation (>2010), history of maternal or infant PMTCT exposure, abacavir-based infant starting regimen and WHO clinical disease stage 3 or 4 were factors associated with unsuppressed VL by 12 months on ART. In multivariable models, pre-treatment VL of >1 million copies/ml [adjusted OR (aOR), 1.75; 95% CI: 1.02–2.98] and CD4% of <25% (aOR: 1.47, 95% CI: 0.99-2.28) were associated with an increased likelihood not achieving viral suppression by 6 months on ART (Table 2). Furthermore, compared to starting ART in 2006-2009, initiation in later periods were associated with greater than 2-fold risk of failure at 12 months (aOR: 2.24, 95% CI: 1.06-4.72 in 2010-2012 and aOR: 2.60, 95% CI: 1.17-5.76 in 2013-2016). Additionally, exposure to maternal or infant PMTCT (aOR: 1.76, 95% CI:0.98-3.18) and WHO clinical disease stage III/IV (vs I/II) (aOR: 1.35, 95% CI: 1.08-1.68) were also associated to viral non-suppression by 12 months on ART (Table 3).

Discussion

In this study of infants initiating first-line combination ART at ≤3 months of age in routine HIV treatment programmes across South Africa, 56% achieved viral suppression by six months on ART and 65% by twelve months. We observed a trend towards poorer viral suppression in recent calendar periods of ART initiation, while immunologic outcomes were similar across calendar period. In addition, the likelihood of not achieving viral suppression at six months increased with pre-treatment VL >1 million copies/mL and CD4 <25% at ART initiation while ART initiation after 2010 (intermediate and later periods), previous maternal or infant PMTCT exposure and WHO disease stage III/IV and being underweight at ART start were associated with viral load >400 copies/ml by twelve months on ART. Our findings demonstrate suboptimal virologic responses among HIV-positive infants, despite earlier ART initiation and a reduction in the prevalence of severe disease characteristics.

Comparison with viral suppression rates in other studies is challenging due to high variations in viral suppression threshold definitions. Some studies assessing infants starting ART <6 months of age demonstrated similar findings to ours A study of infants in Kenya showed that only 31% of infants were suppressed <250 copies/ml [8], while three cohorts from South Africa showed <40% of infants were suppressed <50 copies/ml.[17] It is important to note that due to high levels of viral replication and an underdeveloped functional immune system in the first few weeks of life, infants may not achieve initial suppression within 6 months of treatment.[11] Our finding that only 65% of infants were suppressed after one year on ART is concerning. Several similar studies have reported higher levels (>70%) of viral suppression by one year on ART. [24-26] Conversely, one study in Southern Africa reported a lower 12-month suppression rate of 56% .[12] It is important to note however that all these studies included infants who started ART up to 12 months of age, whereas we restricted our study to infants who initiated ART within 12 weeks of age.

Although similarly poor virologic response among infants have been previously reported [8, 12, 18], our study also demonstrates poorer viral response to ART among early-treated infants in more recent calendar years. This contrasts with evidence from high income countries which show substantial improvements in viral suppression rates over time.[27, 28] Suboptimal short-term virologic suppression in infants who initiated ART ≥2013 compared to earlier years raises major concerns, especially as infants starting in recent years had higher CD4%, lower VL and overall less severe disease at ART initiation. Studies suggest that lower viral load and higher CD4% at ART initiation are associated with faster time to virologic suppression.[29] While there are several possible explanations for our findings, interpreting our findings is challenging as our analysis is limited to those surviving on ART. With the increased emphasis on early diagnosis including birth PCR testing and immediate ART in recent years, many infants in SA initiate ART within the first few days of life. It is likely that the later-period cohort includes several infants with HIV who previously would have died before HIV diagnosis or ART start, or would have started ART later with lower survival on ART. These infants may also be at risk of poorer virologic outcomes, therefore targeted interventions beyond early ART may be necessary to improve virologic response. In addition, the number of infants with available VL was low at 6 months, emphasising the need for strengthening HIV treatment and monitoring in infants who are at risk of low VL suppression.

Furthermore, there is a likely impact of changing socio-demographic characteristics of caregivers and infants where an infant acquires HIV despite more robust VTP regimens. Considering the widespread access to VTP in South Africa especially since 2013, women whose infants become HIV infected may have different risk factors for poorer adherence than those from the previous era when ART was not universally available. This in turn results in increased maternal viral load, risk of infection in breastfeeding infants. Thus, representing a changing demographic in comparison to mothers to infected infants in earlier periods where limited VTP options were available. Achievement of viral suppression in children has been strongly linked to care giver adherence.[30]

Suboptimal regimen efficacy especially for abacavir-containing ART regimens may also play a role in poorer virologic response observed.[31, 32] The South African treatment guidelines recommended that abacavir replace stavudine in the first-line paediatric ART regimens in 2010. Programmatic data from South Africa, both single site and multi-cohorts, has suggested that early virologic outcomes in abacavir based regimens may be poorer than stavudine-based first line regimens.[16, 33] Also, infants starting on an NVP based regimen are more likely to experience virologic failure compared to those on LPV/r based regimen.[26, 34]

In addition, limited antiretroviral formulations for very young infants and additional risk factors including prematurity, co-morbidities and suboptimal ART adherence may be more common in recent years among infants living with HIV despite widespread VTP. Although we were not able to investigate the effect of tuberculosis co-infection in particular, this can contribute to slow viral suppression in African infants.[35] In this study, a third of infants had no maternal/infant VTP exposure and this proportion increased slightly over time. This raises concern around poor documentation in VTP programmes and infant HIV testing cascade particularly as it highlights that the 1-2% of transmission events occurring are likely among caregivers who may have been infected during pregnancy or who may be non-adherent to treatment.

Similar to earlier studies, the likelihood of not achieving short term viral suppression was greater among infants with very high pre-treatment VL (VL >1 million) and low CD4% (<25%) at ART start.[12, 36] Since HIV-PCR rather than VL is now used for both initial and confirmatory diagnostic testing among infants, VL at ART initiation is not routinely measured.[37] However, obtaining pre-treatment VL for infants and young children may be necessary in order to assist with the short term monitoring of VL results. Also, identifying infants with high pre-treatment viral load particularly >1 million copies/ml, may serve as a proxy for mothers and caregivers who need targeted interventions for adherence and psychosocial challenges. Evidence suggests that community-based adherence support is associated with significant improved VL suppression in children on ART.[38] Age at ART start was not associated with failure to suppress (1-month-old vs. 2-3 months old). This finding may be due the inclusion of only infants <3 months old in this study and survivor bias in our study population. To our knowledge there are no cohort studies of infants in routine care RLS that assessed the impact of age on virologic and immunologic outcomes among infants starting ART below 3 months of age. Other studies found an association with younger age (<12 months and <6 months) and lower odds of viral suppression.[8, 18] In contrast, ART initiation before 6 months of age (compared to >6 months) has been associated with later sustained virologic control after initial suppression.[17]

The use of observational cohorts of infants enrolled in routine HIV care in the public and private health sectors in South Africa, allowing us to assess responses to ART among infants initiating care outside of research-controlled environments, is a major strength of this study. In addition, we present findings from an established early infant diagnosis system with birth PCR implemented since 2015 allowing us to report on outcomes of very young infants initiating ART. However, our study has several limitations. We used three calendar periods as a proxy for changes in WHO guidelines, nevertheless these periods may not exactly reflect implementation of guidelines in South Africa which may have been delayed. In addition, the use of a viral load cut-off of <400 copies/ml across calendar periods may have overestimated viral suppression levels in recent years considering that low level pre-treatment viral loads in recently infected infants are increasingly common.[39] Also, due to reliance on routine data, we had some missing data at ART initiation such as VL load measures at six months, maternal characteristics especially regimen and viral suppression, PMTCT exposure and infant antiretroviral formulation. Furthermore, our population may be influenced by selection bias as infants included in the analysis were those who survived and had key measures at six months after starting ART.

Conclusions

This study demonstrates that infants continue to be vulnerable to poor viral outcomes on ART, which, if anything seem to have worsened in the most recent calendar period. While this may reflect a selection bias with more infants in recent calendar years being diagnosed and accessing ART who previously would have died, it shows that in the context of early infant diagnosis and universal treatment, the third 90% target in infants will not be achieved without urgent efforts to improve formulations and interventions to support optimal outcomes in this vulnerable group.

Competing interests

Authors have no competing interests to declare.

Authors' contributions

VI, KT and MAD conceptualized and designed the study. VI analysed the data and wrote the first draft of the manuscript with critical input from all authors. All authors reviewed and approved the final manuscript.

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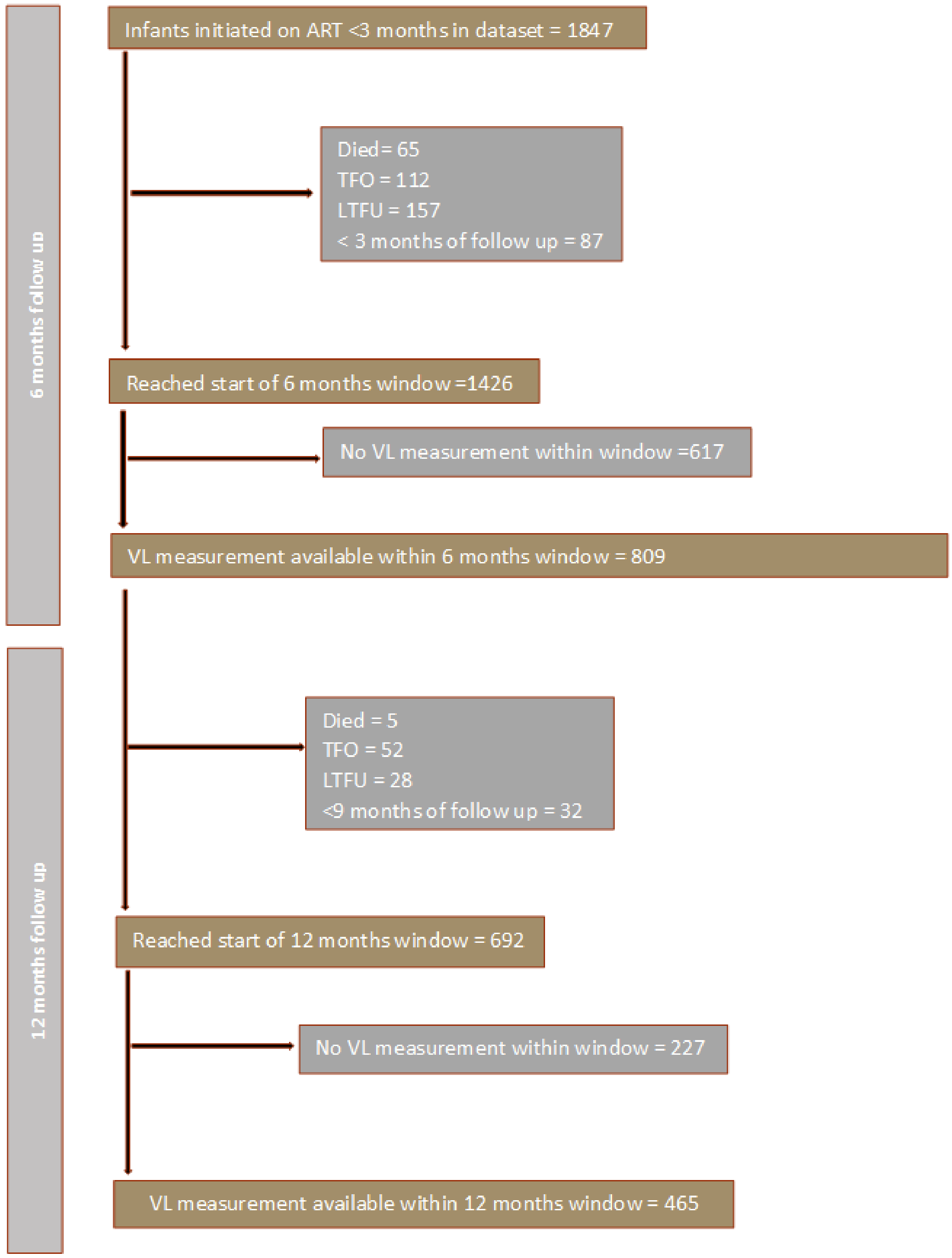


Figure 5-1. Flow chart describing patient selection into analysis at 6 and 12 months on antiretroviral therapy

Footnotes: VL; Viral load, ART; Antiretroviral therapy, LTFU; Lost-to follow-up, TFO; Transferred out

Table 5.1. Pre-treatment characteristics of HIV-positive infants by calendar period of antiretroviral therapy initiation

Characteristics	Total N=809	2006-2009 N= 230	2010-2012 N=254	≥2013 N=325	p-value*
Age (days), median (IQR)	53 (24-71)	59 (44-74)	58 (37-72)	34 (1-64)	<0.001
Age category (days), n (%)					
<30	231 (28.5)	25 (10.8)	50 (19.6)	156 (48.0)	<0.001
31-60	256 (31.6)	97 (42.2)	87 (34.6)	72 (22.1)	
61-90	322 (39.8)	108 (46.9)	117 (46.1)	97 (30.1)	
Female, n (%)	453 (56.0)	117 (50.6)	150 (59.1)	186 (57.2)	0.164
Absolute CD4 count (cells/µL)	1332 (526-2068)	854 (380-1708)	1532 (737-2216)	1540 (697-2143)	<0.001
CD4 Percentage, median (IQR)	27 (18-38)	21 (14-32)	27 (20-38)	32 (23-43)	<0.001
Log viral load, median (IQR)	5.8 (4.7-6.4)	5.8 (5.3-6.4)	6.0 (5.1-6.6)	5.4 (4.0-6.3)	<0.001
Viral load (cpm), n (%)					
<100,000	158 (19.5)	34 (14.8)	40 (15.7)	84 (25.8)	<0.001
100,000 -1 Million	166 (20.5)	68 (29.6)	48 (18.9)	50 (15.4)	
>1 Million	226 (27.9)	73 (31.7)	85 (33.5)	68 (20.9)	
Missing	259 (32.0)	55 (23.9)	81 (32.0)	123 (37.8)	
WHO disease stage, n (%)					
I/II	219 (27.1)	26 (11.3)	64 (25.2)	129 (39.7)	
III/IV	312 (38.5)	157 (68.3)	85 (33.5)	70 (21.5)	<0.001
Missing	278 (34.4)	47 (20.4)	105 (41.4)	126 (38.8)	
WAZ, n (%)					
≤ -2	256 (31.6)	114 (49.6)	77 (30.3)	65 (20.0)	<0.001
> -2	197 (24.3)	48 (20.8)	70 (27.5)	79 (24.3)	
Missing	356 (44.0)	68 (29.5)	107 (42.1)	181 (55.6)	
PMTCT Exposure, n (%)					
No	327 (40.4)	94 (40.9)	85 (33.5)	148(45.5)	0.013
Yes	332 (41.0)	86 (37.4)	115 (45.3)	131 (40.3)	
Unknown	150 (18.5)	50 (21.7)	54 (21.2)	46 (14.2)	
Initial Regimen, n (%)					
ABC/3TC/LPV/r	30 (48.2)	5 (2.2)	206 (81.8)	169 (53.4)	<0.001
AZT/3TC/NVP	89 (11.2)	5 (2.2)	2 (1.0)	82 (25.9)	
AZT/3TC/LPV/r	100 (12.6)	54 (23.5)	10 (3.9)	36 (11.4)	
D4T/3TC/LPV/r	184 (23.3)	154 (66.9)	27 (10.7)	3 (1.0)	
Other	36 (4.7)	3 (1.4)	7 (2.8)	26 (8.3)	

IQR; Interquartile range, WHO; World Health Organization clinical disease stage, WAZ; Weight-for-age Z-score, D4T; Stavudine, 3TC; Lamivudine, ABC; Abacavir, NVP; Nevirapine, LPV/r; Ritonavir-boosted lopinavir, PMTCT; Prevention of mother to child transmission of HIV drug regimen *P-values are obtained from Chi-square and Kruskal Wallis tests for categorical and numerical variables respectively

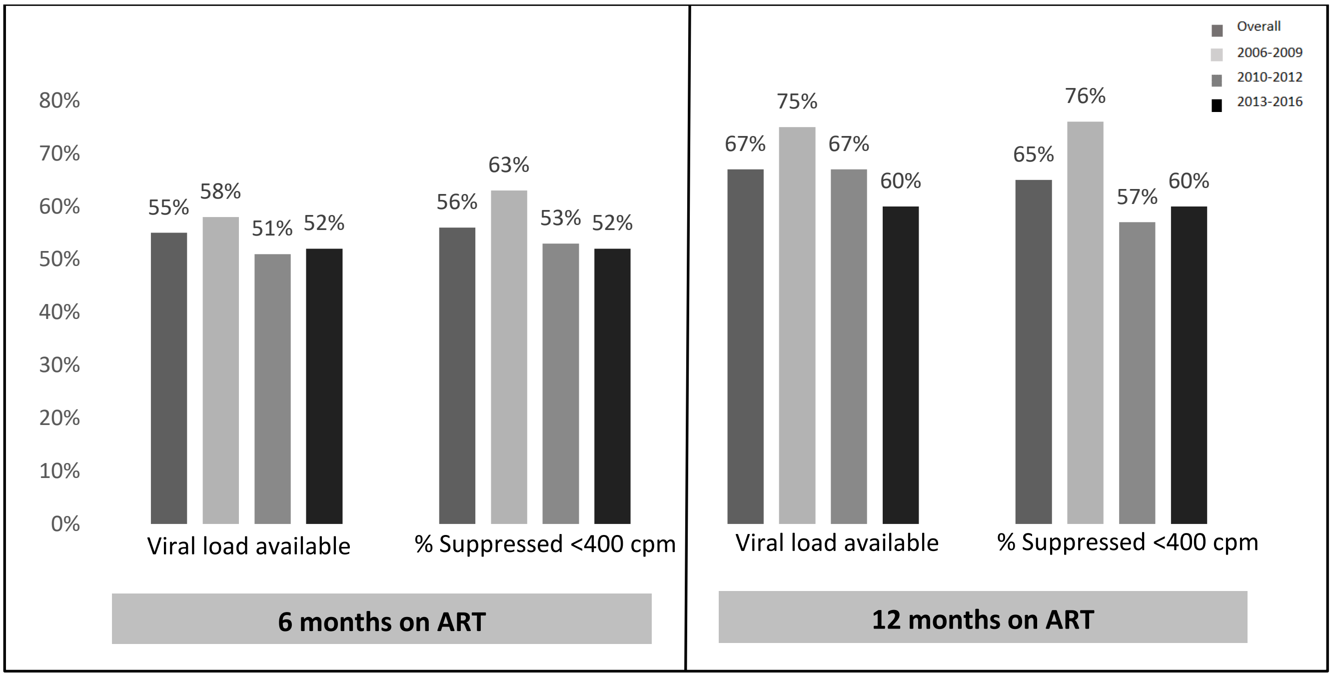


Figure 5-2. Viral suppression at 6 and 12 months among infants starting antiretroviral therapy before 3 months of age in South Africa

Table 5.2. Factors associated with unsuppressed viral load (>400 copies/ml) by 6 months after ART initiation

Characteristics	Univariable			Multivariable		
	OR	95% CI	p-value	AOR	95% CI	p-value
Age (days)						
<30	1			1		
31-60	1.33	0.92-1.93	0.124	1.19	0.74-1.91	0.457
61-90	1.53	1.08-2.18	0.016	1.28	0.78-2.10	0.312
Female	0.81	0.61-1.08	0.161	0.77	0.55-1.06	0.117
ART initiation year						
2006-2009	1			1		
2010-2012	1.51	1.04-2.18	0.026	0.88	0.45-1.71	0.717
≥2013	1.54	1.08-2.19	0.015	1.20	0.60-2.38	0.590
Viral load (copies/mL)						
<100,000	1			1		
100,000-1 Million	1.46	0.91-2.33	0.110	1.32	0.77-2.28	0.305
>1 Million	2.00	1.33-3.19	0.001	1.75	1.02-2.98	0.039
CD4 percentage						
≥25.0%	1			1		
<25.0%	1.31	0.91-1.90	0.141	1.47	0.99-2.28	0.051
PMTCT exposure						
No	1			1		
Yes	1.06	0.78-1.45	0.687	1.05	0.68-1.62	0.805
Unknown	0.75	0.50-1.12	0.164	0.48	1.97-1.19	0.115
Initiation regimen						
D4T/3TC/LPV/r	1			1		
ABC/3TC/LPV/r	1.89	1.15-3.11	0.012	1.81	0.72-4.53	0.190
AZT/3TC/NVP	1.40	0.68-2.87	0.353	1.76	0.65-4.80	0.259
AZT/3TC/LPV/r	0.81	0.39-1.68	0.569	0.31	0.36-1.91	0.655
Other	0.42	0.18-0.98	0.046	0.33	0.12-0.91	0.033
WHO disease stage						
Stage I/II	1			1		
Stage III/IV	1.22	1.09-1.38	0.001	1.14	0.97-1.33	0.093
WAZ						
>-2	1			1		
≤ -2	1.01	0.86-1.20	0.824	0.77	0.46-1.31	0.334

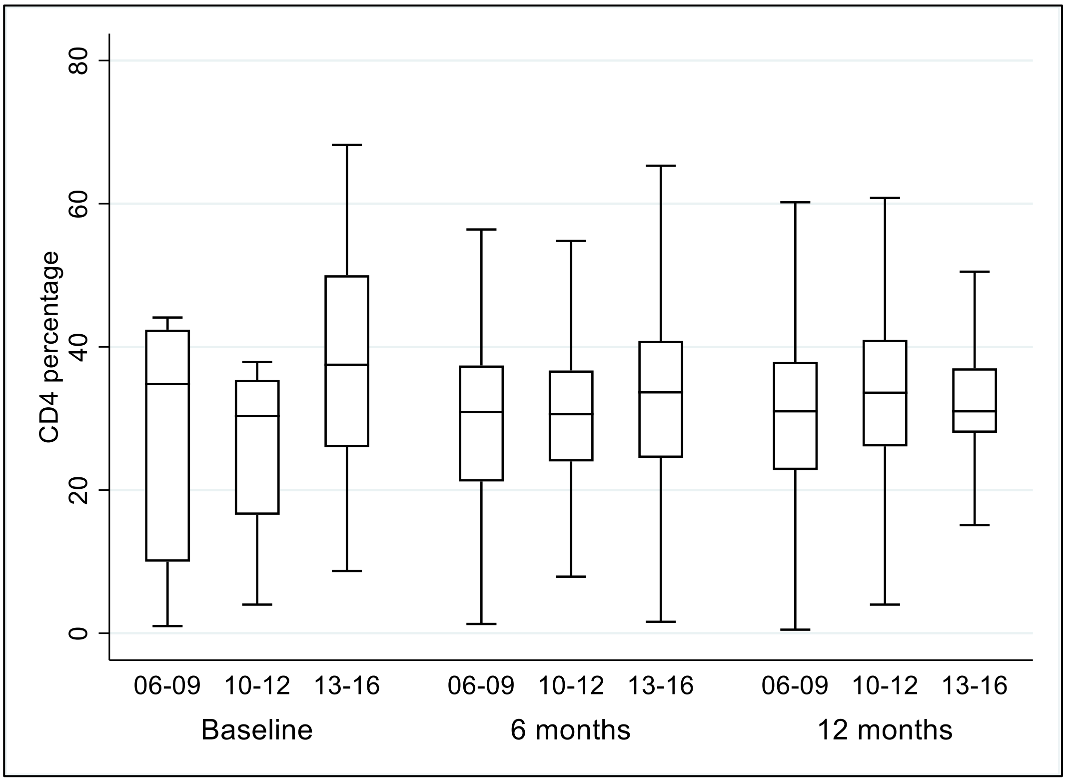
OR; Odds ratio, AOR; Adjusted odds ratio, 95% CI; 95% confidence interval, WHO; World Health Organization clinical disease stage, WAZ; Weight-for-age Z-score, D4T; Stavudine, 3TC; Lamivudine, ABC; Abacavir, NVP; Nevirapine, LPV/r; Ritonavir-boosted lopinavir, PMTCT; Prevention of mother to child transmission of HIV drug regimen **Model was adjusted for cohort

Table 5.3. Factors associated with unsuppressed viral load (>400 copies/ml) by 12 months after ART initiation (n=465)

Characteristics	**Univariate**			**Multivariable**		
	OR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**
Age category (days)						
0-31	1			1		
31-60	0.72	0.42-1.21	0.222	0.73	0.38-1.40	0.356
61-90	0.96	0.59-1.58	0.891	0.90	0.46-1.73	0.754
Female	0.83	0.56-1.23	0.368	0.78	0.50-1.21	0.271
ART initiation year						
2006-2009	1			1		
2010-2012	2.45	1.50-4.03	0.000	2.24	1.06-4.72	0.033
≥2013	2.16	1.31-3.56	0.002	2.60	1.17-5.76	0.018
Viral load (copies/mL)						
<100,000	1			1		
100,000-1Million	1.15	0.61-2.15	0.652	1.39	0.68-2.84	0.352
>1 Million	1.70	0.95-3.04	0.071	1.75	0.88-3.47	0.107
CD4 cell percentage						
≥25.0%	1			1		
<25.0%	1.34	0.86-2.07	0.182	1.55	0.91-2.63	0.102
PMTCT exposure						
No	1			1		
Yes	2.03	1.31-3.15	0.001	1.76	0.98-3.18	0.058
Unknown	1.35	0.78-2.35	0.273	0.86	0.23-3.23	0.828
Initiation regimen						
D4T/3TC/LPV/r	1			1		
ABC/3TC/LPV/r	2.25	1.26-4.03	0.006	1.28	0.54-2.98	0.566
AZT/3TC/NVP	1.08	0.90-0.25	0.908	0.75	0.12-4.74	0.760
AZT/3TC/LPV/r	1.24	0.47-3.24	0.654	1.01	0.35-2.87	0.974
Other	1.04	0.31-3.46	0.946	0.94	0.24-0.36	0.932
WHO disease stage						
Stage I/II	1			1		
Stage III/IV	1.39	1.18-1.64	0.000	1.35	1.08-1.68	0.006
WAZ						
>-2	1			1		
≤ -2	0.85	0.68-1.08	0.201	0.65	0.37-1.12	0.123

OR; Odds ratio, AOR; Adjusted odds ratio, 95% CI; 95% confidence interval, WAZ; Weight-for-age Z-score, D4T; Stavudine, 3TC; Lamivudine, ABC; Abacavir, NVP; Nevirapine, LPV/r; Ritonavir-boosted lopinavir, PMTCT; Prevention of mother to child transmission of HIV drug regimen

**Model was adjusted for cohort



		2006-2009	2010-2012	2013-2016	p-value
6-month CD4%					
CD4 measurement available	625	220	214	191	
Median CD4 percentage	30 (22-37)	29 (21-36)	30 (23-36)	31 (23-38)	0.161
12-month CD4%					
CD4 measurement available	373	148	122	103	
Median CD4 percentage	31 (25-39)	31 (24-39)	33 (26-40)	31 (25-37)	0.266

Figure 5-3. Median CD4 percent of infants at ART initiation, 6 and 12 months on ART by calendar period of antiretroviral therapy initiation

Supplementary Material

Table S1: Characteristics of HIV-positive infants who did not achieve suppression at both six and twelve months on antiretroviral therapy (n=116)

Characteristics	N	Frequency
Age (days), median	116	9.5 (6.1-12)
Female, n (%)	116	57 (49.1)
ART initiation year, n (%)	116	
2006-2009		21 (18.6)
2010-2012		48 (41.3)
≥2013		47 (40.5)
Absolute CD4	83	1201 (541-2130)
CD4 Percentage, median	86	24.8 (18.3-36.4)
Viral load (cpm), n (%)	87	
<100,1000		17 (19.5)
100,000 -1 Million		24 (27.5)
>1 Million		46 (52.8)
WHO stage III/IV, n (%)	58	35 (60.0)
WAZ, n (%)	63	
≤ -2		39 (61.9)
>- 2		24 (38.1)
PMTCT Exposure, n (%)	116	
No		37 (31.9)
Yes		58 (52.6)
Unknown		1815.5)
Initial Regimen, n (%)	47	
LPV/r based regimen		42 (89.3)
NVP based regimen		2 (4.2)
Other		3 (6.4)

WAZ; Weight-for-age Z-score, NVP; Nevirapine, LPV/r; Ritonavir-boosted lopinavir, PMTCT; Prevention of mother to child transmission of HIV drug regimen

Table S2: Characteristics of infants at ART initiation by viral suppression status at 6 months on antiretroviral therapy

Characteristics at ART initiation	Suppressed N= 455	Not suppressed N=354	p-value*
Age (days), median	50 (16-68)	55 (32-73)	0.019
Female, n (%)	264 (58.0)	189 (41.7)	0.188
ART initiation year			
2006-2009	146 (63.4)	84 (36.5)	0.030
2010-2012	136 (53.5)	118 (46.6)	
≥2013	173 (53.3)	152 (46.7)	
Absolute CD4	**321**	**223**	0.553
	1363 (487-2028)	1267 (555-2077)	
CD4 Percentage, median	**301**	**231**	0.171
	28.3 (18.9-38.7)	25.9 (18.5-36.9)	
Viral load (cpm), n (%)	**309**	**241**	
<100,1000	104 (65.8)	54 (34.1)	0.004
100,000 -1 Million	95 (57.2)	71 (42.7)	
>1 Million	110 (48.7)	116 (51.3)	
Log viral load, median	**309**	**241**	
	5.7 (4.5-6.3)	6.0 (5.3-6.4)	<0.001
WHO stage III/IV, n (%)	**313**	**205**	
	185 (59.2)	127 (40.7)	0.002
WAZ, n (%)	**264**	**189**	
≤ -2	145 (55.3)	108 (58.1)	0.257
>- 2	120 (60.9)	77 (39.1)	
PMTCT Exposure, n (%)	**455**	**354**	
No	180 (55.1)	147 (44.9)	0.149
Yes	180 (54.2)	152 (45.7)	
Unknown	91 (20.5)	55 (15.9)	
Initial Regimen, n (%)	**448**	**347**	0.005
LPV/r based regimen	366 (81.8)	299 (86.1)	
NVP based regimen	53 (11.9)	42 (12.2)	
Other	29 (6.5)	6 (1.7)	

WAZ; Weight-for-age Z-score, NVP; Nevirapine, LPV/r; Ritonavir-boosted lopinavir, PMTCT; Prevention of mother to child transmission of HIV drug regimen

Chapter 6: Long-term virological outcomes in children initiating early antiretroviral therapy at <1 year of age in South Africa.

Relevance of this paper to the thesis:

This manuscript addresses the fourth objective of this thesis by exploring the long-term outcomes of universal ART in infants. There is an urgent need to understand the ongoing implications of initiating early infant ART on long-term outcomes, specifically virologic suppression. The paper therefore focuses on long-term viral suppression among infants starting ART during infancy (<1 year of age), describing viral suppression up to five years on ART and the predictors of virologic non-suppression over time.

Contribution of the student and co-authors:

I conceived the design of this analysis with support from MD and KT. I conducted the analysis and drafted the manuscript. All co-authors reviewed the manuscript and provided critical input. All authors were involved in the final draft of the manuscript.

Publication status: Being prepared for submission

Long-term virological outcomes of children initiating early antiretroviral therapy at <1 year of age in South Africa

Abstract

Background

Given the expansion of paediatric HIV treatment initiation criteria, an increasing number of children are starting lifelong antiretroviral therapy at a younger age. However, there is limited data on the long-term outcomes beyond two years of follow-up for children starting antiretroviral therapy (ART) during infancy in resource-limited settings. Therefore, we described the long-term virological outcomes of early-treated children living with HIV (CLHIV) in South Africa.

Methods

Using a retrospective cohort study design, we included data from CLHIV enrolled within the International epidemiology Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) and who initiated ART <12 months of age between 2006-2014. We assessed viral suppression (<400 copies/ml) up to five years on ART and examined predictors of viral suppression using GEE logistic regression models.

Results

Overall, 2969 (51.9% female) CLHIV were included with a median follow up of 41 months (IQR 25-70). At ART initiation, children had a median age of 5.0 months (3.2-7.9) and a median CD4% of 20% (13-29). Seventy-four percent of children were at WHO clinical disease stage three or four, and nearly half (46.7%) had viral load >1 million copies/ml. Overall, 55.7% (95 % CI: 57.3-57.7), 71.5% (68.7-74.1) and 76.0% (72.9-78.9) of children were virally suppressed at 1, 3 and 5 years on ART respectively. Across age groups at ART initiation (0-3, 4-7 and 8-12 months), there was a similar trend towards an increasing proportion of children virally suppressed annually over five years on ART. However, children staring ART between 0-3 months were less likely to achieve viral suppression at all timepoints. Based on multivariable binomial GEE regression analysis with multiple imputation of missing data, having a CD4% of ≤15 and WHO clinical disease stage three or four at ART start was associated with an increased risk of virological non-suppression over time.

Conclusion

Findings suggest that achieving good long-term viral suppression in children starting ART during infancy is feasible in routine care settings while emphasising the role of severe HIV disease at ART initiation in preventing optimal long-term outcomes. Results highlight the importance of early infant ART and the need to focus on addressing the challenges related to neonatal ART initiation in resource-limited settings.

Introduction

In 2019, an estimated 240,000 children under 14 years of age were living with HIV, 10,000 newly acquired the infection, and 4100 died of AIDS-related conditions in South Africa.[1] Infants <1 year of age are the most vulnerable to rapid HIV disease progression and death.[2] Given the evidence on the benefits of earlier ART initiation for reducing mortality and morbidity, in 2008, the World Health Organisation (WHO) recommended immediate treatment of all newly diagnosed infants <12 months regardless of their WHO clinical stage or CD4 cell count.[3] As a result, there has been a scale-up of early infant diagnosis and treatment practices in many countries within sub-Saharan Africa, giving rise to an increasing number of infants who start life-long ART at much younger ages.[1] South Africa, in particular, has the most extensive early infant diagnosis program globally, with >95% of HIV-exposed infants tested before two months of age.[4] The short-term benefits of early infant ART are well documented. Yet, little is known about the long-term effectiveness of ART among early-treated infants enrolled in routine care in resource-limited settings.[5]

The success of life-long ART depends on the achievement and maintenance of virological suppression. Compared to adults, infants and young children bear additional complexities relating to HIV treatment due to factors such as limited antiretroviral drug formulations, frequent weight-based dose adjustment and caregiver dependence. While 12-month viral suppression rates have been reported from treatment programs in Africa[5, 6], data on virological outcomes >3 years on ART is scarce, particularly among children initiating ART during infancy. The majority of published long-term data is from paediatric cohorts in high-income countries, showing reasonable virologic suppression rates of >70%.[7-10] Nevertheless, a clinical trial in South Africa reported excellent virologic suppression of >80% after nearly five years.[11] However, observational studies show high variation in viral suppression levels ranging from 26% to 76% at up to 24 months on ART.[12-16] Despite the survival benefit of early ART, these findings suggest that a substantial proportion of infants fail to suppress on ART. Poor long-term outcomes, including treatment failure, therefore remain a growing concern.

Understanding the ongoing implications of early infant ART on long-term virological outcomes will provide valuable insights for paediatric care, especially in settings where viral load monitoring capacity is suboptimal. Therefore, we described the long-term virological suppression up to five years on ART and assessed predictors of virological non-suppression among children initiating first-line ART at <1 year of age in the International epidemiology Databases to Evaluate AIDS – Southern Africa Collaboration (IeDEA-SA) cohorts in South Africa.

Methods

Study population

We conducted a retrospective cohort analysis of infants living with HIV who started ART between January 2006 and December 2014. We included infants who had a confirmed HIV diagnosis and were <12 months old at ART initiation. We excluded children who had <1 year of follow-up and children who did not have a viral load measure after ART initiation. Clinical data at ART initiation and through follow-up, which form part of the routine treatment and monitoring of HIV data, were collated at IeDEA-SA clinical sites by cohort investigators. Anonymised data were then transferred to the IeDEA-SA Data Centre using a standard transfer protocol. Each cohort has institutional and ethical approval to contribute data to IeDEA-SA for analysis. [17] Overall ethical approval for data analysis was obtained from the Human Research Ethics Committee of the University of Cape Town, South Africa.

Outcome and key variable definitions

The primary outcome of this study was viral suppression which we defined as having a viral load below 400 copies per ml. In addition, we assessed trends in viral suppression in each year of follow-up from the start of ART and examined predictors of virological non-suppression (≥400 copies per ml) over time. We defined LTFU as no contact with the care site for one year before the cohort closure date, with the last visit date considered as the date of LTFU. Transfer out was defined based on the documented date of transfer to other facilities.

Covariates considered at the start of ART were age, sex, CD4 cell percentage, viral load, WHO clinical disease stage, anthropometric measures, calendar year at the start of ART, duration on ART and initial regimen. The calendar year of ART start was categorised into 2006-2010 and 2011-2014, periods before and after the WHO 2010 guideline for universal infant ART. Age at ART start was categorised *a priori* into three groups; 0-3, 4-7 and 8-12 months, to evaluate risk among children starting early ART before three months of age compared to later ART. WAZ was calculated using STATA macros downloaded from the WHO (www.who.int). They were calculated based on the WHO 2007 growth standards. Biologically implausible values for z-scores, as flagged by the macros, were excluded from the analysis. Children with WAZ <-2 were considered underweight according to the WHO definitions.

Statistical analysis

We summarised continuous variables using mean (standard deviation) or median (Interquartile range) as appropriate and categorised them based on clinical relevance. In addition, we summarised categorical variables using proportions. Between-group comparisons were examined using Chi-square and Kruskal-Wallis tests. Proportions with viral suppression over time were examined cross-sectionally per year on ART for up to five years of follow up. We used generalized estimating equations (GEE) logistic regression models to explore the trends in viral suppression for repeated viral load measures over time. Models were adjusted for clustering at the site level and for the time at risk. Taking into account the effect of selection bias due to incomplete follow-up of some children, we repeated the analysis, including (i) only children with two or more repeated viral load tests and with three years or longer of follow up since ART initiation and (ii) only children who had at least one viral load measure in each year of follow-up for at least five years. We also examined the effect of age at ART start and other predictors on the risk of virological non-suppression (VL $\geq$ 400 copies/ml). To avoid loss of information and potentially biased estimates because of missing data, we imputed missing values of predictor variables using multiple imputation methods. We conducted a complete-case analysis, thereby accounting for possible differences between observed and missing data. P values of <0.05 were considered to be significant. We analysed all data using STATA, version 15 (StataCorp).

Results

A total of 4,838 infants <1 year of age started ART between January 2006 and December 2014. We excluded 1527 children who had <1 year of follow up on ART and 342 children with no viral load measure. Therefore, 2969 children were included in this study. Children were followed up until database closure on 21 February 2019, with a median follow up of 41 months (IQR 25-70). Thus, 1490 (57.2%) children had three years or longer follow-up since ART initiation. The median age at ART initiation was 5.0 months (3.2-7.9), and the median CD4% was 20 (13-29). Seventy-four percent of children were at WHO clinical disease stage three or four, and nearly half had a viral load >1 million copies/ml. A quarter of children were severely underweight (WAZ ≤ -3), and two-thirds started ART before 2010. Two-thirds of infants started ART between 4-7 months of age, while viral load at ART start did not significantly vary across age at ART start (Table 1).

Overall, viral suppression was achieved by 55.7% (95% CI: 57.3-57.7), 71.5% (68.7-74.1) and 76.0% (72.9-78.9) of children was observed at one, three and five years on ART, respectively. There was a similar trend towards increasing levels of viral suppression over time across all age groups at ART initiation. However, children staring ART between 0-3 months were less likely to be virally suppressed at all time points (Figure 1a). Upon restricting the analysis to 1490 children who had three years or longer of follow-up, the proportion virally suppressed remained similar at 57.8% (95% CI: 55.0-60.5) at one year, 71.4% (95% CI: 68.7-74.1) at three years and 76.0% (95% CI: 72.9-78.9) at five years (Figure 1b). Among 462 children with at least one viral load measure in each of the five years of follow up, viral suppression was achieved by 53.6% (95% CI: 49.0-58.2) at one year, 73% (95% CI: 69.1-77.2) at three years and 76% (95% CI: 72.9-78.9) at five years on ART (Figure 1c). The trend in viral suppression levels observed across age groups at ART initiation categories remained consistent for the two subgroups.

Based on multivariable binomial GEE regression analysis with multiple imputation of missing data, having a CD4% ≤15 and WHO clinical disease stage three or four at the start of ART was associated with an increased risk of virological non-suppression over time. Starting ART >3 months of age was associated with a reduced risk of virological non-suppression. The estimated relative risk did not change substantially after re-running the regression analysis with complete case data analysis (Table 2).

Discussion

To our knowledge, this is the first cohort study to report on long-term HIV viral load data in African children starting first-line ART at <1 year of age in routine care settings. Seventy-six percent of children achieved viral suppression by five years on ART using a cut-off of <400 copies per ml. We observed a trend towards good long-term suppression levels over time, in the overall study population and according to the age of ART initiation (0-3,4-7 and 8-12 months). However, fewer infants who started ART <3 months achieved virologic suppression at all time points through five years on ART. This finding was supported by the multivariable regression analysis, which showed that older age (>3 months) at ART start was associated with a reduced likelihood of virologic non-suppression over time. Severe HIV disease characteristics at ART start; low CD4 percent (≤15%) and being at WHO clinical disease stage three or four were associated with virological non-suppression.

Our finding of >70% of infants achieving virologic suppression by five years on ART show promise of good long-term early infant ART outcomes, similar to results described in high-income countries.[7] Similar findings have also been suggested by the CHER trial, which described high viral suppression levels of 83% after nearly five years on ART.[11] Nevertheless, there is significant heterogeneity in reported findings of viral suppression from observational studies in SSA. One study reported a virologic suppression rate of 83% by 12 months on ART among infants in Uganda.[16] Another study from a similar setting reported a probability of virologic suppression of 56% by 18 months.[13] Earlier studies from South Africa presented a range of 26-56% of virologic suppression.[14, 15] but at a shorter duration on ART. Given the multiple challenges that infants face in adhering to ART, including limited formulations, frequent dose adjustments and caregiver dependence, it is reassuring that such a high proportion achieved viral suppression in these routine care cohorts. Nonetheless, our estimates fall short of the UNAIDS 90–90-90 treatment targets, a strategy to end the global HIV epidemic.

Various factors may explain suboptimal long-term virological suppression levels among children starting ART before three months of age. The biological characteristics of very young infants at ART start have been shown to play a significant role. Infants have been shown to have a slower viral suppression rate compared to older children and a higher risk of virological failure.[18, 19] This delay in initial suppression has been linked to an underdeveloped immune system. Evidence also suggests that infants infected before one month of age have better virologic control than those infected afterwards.[20] It is possible that older children, who have survived the peak mortality period among infected infants (0-3 months of age) [2], were a select group of survivors who were able to mount a more effective immune response. Therefore this survival may be related to improved virologic control due to enhanced immune responses.[21] Our findings reemphasise the need for specific focus and attention needed for infants with HIV in the first three months of life. One of the primary factors centres around suboptimal treatment: limited availability of anti-retroviral for use in the neonatal period, frequent need for changing doses due to weight change, and palatability-related issues of the recommended drugs. These issues could lead to under-dosage and decreased bioavailability. Also, studies have described lower virological effectiveness for children on an abacavir-containing triple NRTI regimen compared to zidovudine, stavudine or a protease inhibitor-based (PI) regimen.[22, 23] Furthermore, infants started on PI-based regimen were described to be at an advantage in terms of virological outcome in comparison with a nevirapine-based regimen.[24] These challenges collectively reinforce the complexity of neonatal HIV management. Better drug formulations specifically for infants are required to address dosage and adherence challenges. An encouraging recent advancement is the approval of dolutegravir (DTG) paediatric dispersible tablets for infants weighing >3 kg and >4 weeks of age. Nevertheless, there is a need for continued efforts to provide infant friendly formulations to improve treatment effectiveness and expand ART access.

Given the improved birth HIV PCR testing in South Africa, there is a need to understand the possible contribution of increasing in-utero infections in this population. A further considered hypothesis is that in-utero exposure to maternal ART, PMTCT prophylaxis and ART through breastmilk may contribute to ART resistance later on in life. Furthermore, caregiver dependence for infants is an essential determinant of treatment outcomes. It has been reported that mothers who experience perinatal transmission struggle frequently with ART adherence and retention in care resulting in inadequate infant viral suppression.[24] The primary drivers of the persistent few perinatal HIV transmissions include maternal HIV acquisition during pregnancy and poor or no ART usage. Therefore, these present risk factors for drug resistance and virologic failure, an ongoing concern for children infected in the era of widespread PMTCT.[25] Understanding the needs of mothers who experience MTCT in the era of widespread ART for prevention and treatment is crucial to achieving optimal infant outcomes.

We also observed an increased likelihood of virologic non-suppression among infants at an advanced stage of HIV in terms of CD4 <15% and WHO clinical disease stage three or four. These factors have commonly been associated with an increased risk of mortality. Therefore this finding substantiates the need for earlier ART before complications and advanced disease, as supported by previous research.[26] Late ART initiation remains a challenge in resource-limited settings, which experience delayed turnaround times for results, challenges with linking infants diagnosed with HIV to sites providing infant ART and limited expertise for neonatal ART treatment. [27]

One major strength of this study is the disaggregation of long-term virologic suppression data by age at ART start, focusing on children starting ART as neonates among whom there is limited data. In addition, presenting data on infants followed up for up to five years in routine care settings is a novel contribution of this study. Limitations of this study include incomplete follow-up, missing data viral load and CD4 at ART initiation and unmeasured confounders such as maternal characteristics not routinely documented in routine care. To account for selection bias due to incomplete follow-up, we conducted a subgroup analysis including groups of infants who were followed up for at least three years and repeated in those with up to five years of follow up and viral load measure each year. Our findings remained consistent across the various populations. Missing baseline data was accounted for by using multiple imputation methods. We could not assess the impact of maternal factors such as the timing of HIV diagnosis and viral load in the perinatal period on the virologic outcomes on infants. Future research needs to consider maternal characteristics, especially in the era of widespread PMTCT access.

In conclusion, our findings provide reassuring evidence of the long-term health benefits of early infant ART in resource-constrained settings, with high suppression rates after five years on ART. However, our findings also highlight important areas for further investigation, such as addressing the gaps in neonatal care, especially in the context of widespread ART for paediatric HIV prevention and treatment.

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Table 6.1 Characteristics of children initiating ART in the first year of life by age at antiretroviral therapy initiation (n=2969*)*

Characteristics	Overall	0-3 months	4-7 months	8-12 months
Female	1542 (51.9)	336 (54.2)	957 (52.4)	248 (47.7)
Median age (months)	5.0 (3.2-7.9)	2.1 (1.4-2.5)	5.1 (3.8-6.8)	10.3 (9.7-11.2)
Median CD4 %	20.0 (13-29)	26 (17-38)	19 (12-28)	17 (12-24)
Median Log_{10} Viral load	5.9 (5.2-6.5)	5.8 (4.9-6.4)	5.9 (5.2-6.4)	5.9 (4.2-6.4)
Viral load category				
<1000	55 (3.0)	14 (3.7)	29 (2.55)	12 (3.9)
1000 - ≤1 Million	915 (50.3)	201 (52.7)	560 (49.3)	154 (51.2)
>1 Million	849 (46.7)	166 (43.8)	548 (48.2)	135 (44.9)
Missing	1150	239	690	221
WAZ				
<-3	576 (37.2)	117 (41.0)	370 (37.0)	89 (33.5)
≥-3 - <-2	290 (18.7)	50 (17.5)	195 (19.5)	45 (16.9)
≥-2	684 (44.1)	118 (41.4)	434 (43.4)	132 (49.6)
Missing	1419	335	1628	256
WHO stage 3 or 4	1232 (74.4)	234 (68.0)	(790 (76.3)	208 (75.1)
Duration on ART (months)				
0-12	110 (3.7)	33 (5.3)	64 (3.5)	13 (2.5)
13-36	1163 (39.2)	282 (45.5)	697 (38.1)	184 (35.2)
>36	1696 (57.1)	305 (49.2)	1066 (58.4)	325 (52.3)
Year of ART start				
2006-2010	1967 (66.2)	327 (52.7)	1260 (70.0)	380 (72.8)
2011-2014	1002 (33.7)	293 (47.3)	567 (3.0)	142 (27.2)

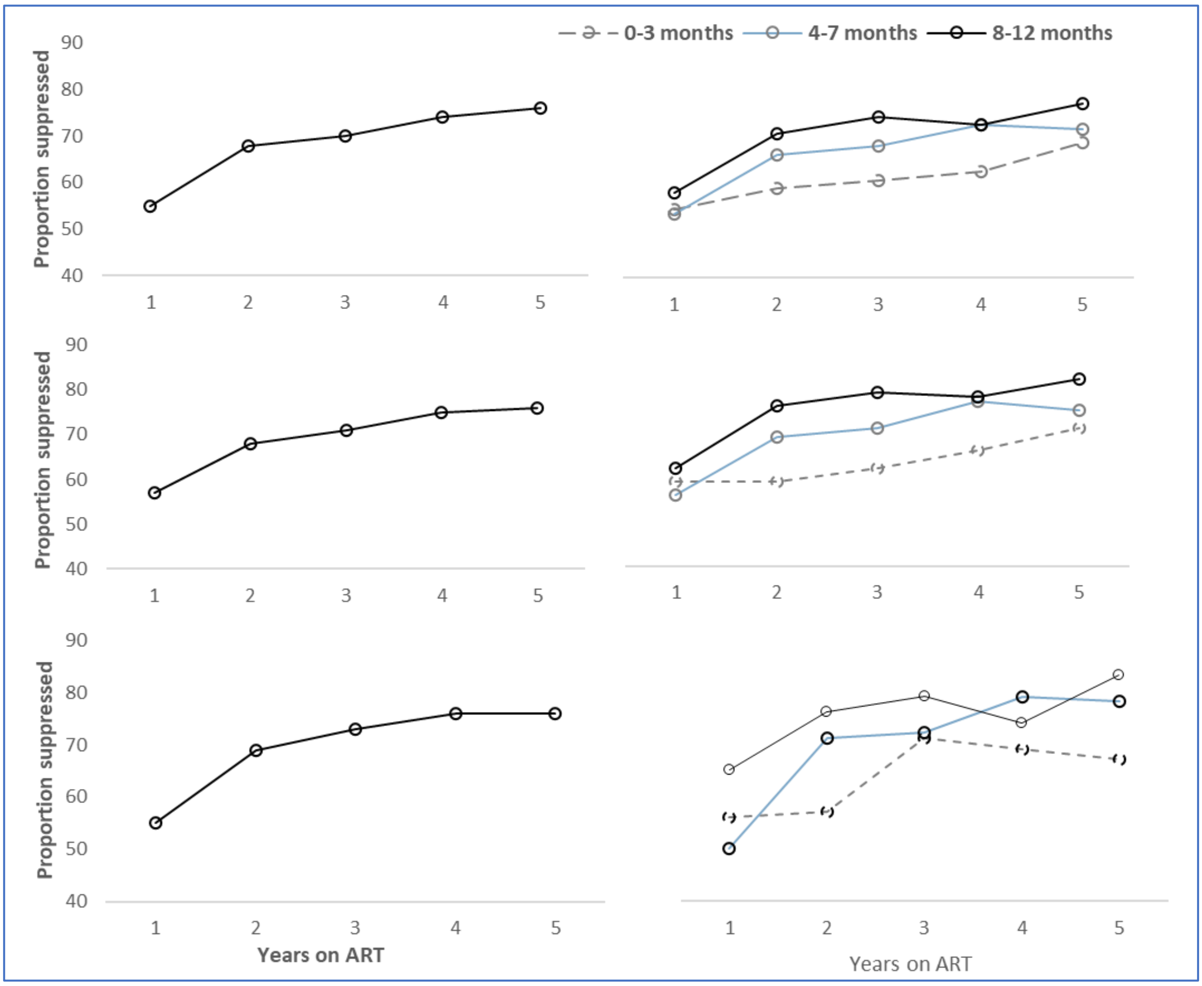

Figure 6-1. (a) Viral suppression rates during 5 years of follow up on ART overall and by age of ART initiation among the overall study population (n=2969) (b) Viral suppression rates during 5 years of follow up on ART overall and by age of ART initiation among children who have ≥2 viral load measures and at least 3 years of follow-up (n=149) (c) Viral suppression rates during 5 years of follow up on ART overall and by age of ART initiation among children who have at least one viral load in each year of follow-up for up to 5 years (n=462)

Table 6.2. Predictors of virological non-suppression in children who started ART <1 year of age in South Africa

	Univariable regression		Multivariable regression			
Characteristics	Crude odds ratio ratio		Complete case odds		Multiple imputation adjusted odds ratio	
	RR	p value	aRR	p value	aRR	p value
Age (days)						
<3 months	1		1		1	
4-7 months	0.82	0.001	0.97	0.898	0.81	0.004
8-12 months	0.64	0.000	0.79	0.561	0.67	0.000
Female	0.88	0.022	1.02	0.900	0.88	0.006
ART initiation year						
2006-2010	1		1		1	
2011-2014	1.32	0.001	0.99	0.976	1.22	0.204
Viral load						
<100,000	1		1		1	
100,000-1Million	0.93	0.738	2.53	0.117	0.92	0.653
>1 Million	1.31	0.134	2.87	0.070	1.17	0.453
CD4 percentage						
>25.0%	1		1		1	
>15 - ≤25.0%	1.05	0.467	0.74	0.164	1.05	0.408
≤15%	1.26	0.010	0.90	0.628	1.28	0.010
WHO disease stage						
Stage I/II	1		1		1	
Stage III/IV	1.59	0.000	1.35	0.180	1.45	0.000
WAZ						
>-2	1		1		1	
≤ -2	1.31	0.000	0.97	0.899	1.12	0.000
Firstline regimen						
3TC/AZT/KLT	1		1			
3TC/D4T/KLT	0.82	0.079	0.86	0.607	0.74	0.043
3TC/ABC/KLT	1.16	0.087	1.22	0.583	1.17	0.358
3TC/AZT/NVP	0.70	0.502	1.00	0.624	0.60	0.382
Other	0.95	0.825	1.06	0.678	1.42	0.222

Adjusted for time at risk and clustering between cohorts

Chapter 7: Discussion and recommendations

7.1 Discussion of key findings

7.1.1 Introduction

This thesis sought to improve the understanding of the association between the changes in WHO and national ART guidelines and outcomes of infants and young children living with HIV in SSA. It analysed trends in key metrics of the paediatric HIV care continuum in the context of universal ART. Specific metrics assessed include timeliness of ART initiation by assessing temporal changes in child characteristics at ART initiation, and measures of ART effectiveness (mortality and viral suppression). Timely diagnosis and treatment of HIV infection before the onset of advanced disease remain an essential component of comprehensive HIV care in children. The four results chapters (3-6), presented as journal papers or manuscripts for submission, include data from infants and young children initiating ART between 2006-2017. This period was a time of successive ART guideline changes resulting in an expansion of access to PMTCT, EID and paediatric ART programmes.

This thesis includes a large cohort of children with HIV in SSA, including one of the first early infant ART cohorts from routine care in South Africa. It offers novel insights into trends in characteristic and outcomes at ART initiation. Chapters 3 and 4 focused on evaluating universal ART expansion for young children in SSA (chapter 3) and infants in South Africa (chapter 4) by assessing the trends in early ART initiation and severe HIV disease at the start of treatment. These chapters also focused on the impact of universal ART guidelines on programmatic outcomes by assessing trends and patterns of mortality and LTFU. Chapters 5 and 6 examined the effectiveness of early infant ART in terms of virological outcomes. Viral suppression is a measure of treatment effectiveness and is key to eradicating the public health burden of the epidemic. Therefore, viral load monitoring is crucial, especially among children in high HIV burden settings. Thus, Chapter 5 focused on temporal trends in the availability of viral load measures and short-term viral suppression, while Chapter 6 describes long-term viral suppression stratified by age at ART initiation and also examines the predictors of virologic non-suppression.

This synopsis provides a summary of (i) findings based on the collective results presented in this work, (ii) strengths and limitations and (iii) recommendations for practice and future studies. As part of the summary, overarching issues raised in relation to the objectives of this thesis and the broader research context will be discussed.

7.1.2 Improvement in ART initiation characteristics

Across calendar periods of ART initiation assessed in Chapter 3 and 4, there was a substantial reduction in the number of infants and young children starting treatment over time from 2006-2017. This finding highlights the success of effective PMTCT programmes in preventing new perinatal infections and the need to focus on the gaps in the care cascade by understanding characteristics of children who still become infected. Therefore, it is essential to consider the characteristics of children starting ART and how these may have evolved over time, as effective PMTCT, EID and EIART practices continue to expand across SSA. It is encouraging that results from this thesis showed a substantial decrease in the median age of infants starting ART in South Africa from 2006-2016. This finding is mainly driven by results presented in Chapter 2, which shows >80% of infants among all infants starting ART within three months of age in SSA were living in South Africa, an upper-middle-income country with high uptake (>90%) of EID for infants within two months of age and birth HIV PCR testing.[4] Indeed, in Southern Africa, it has been shown that the proportions of children < 1-year-old initiating ART is increasing.[5]

In addition, compared to 2006-2009, among all children starting ART under five in SSA there was a doubling of the proportion of infants initiating ART within three months of age between 2013-2016, the majority of whom live in South Africa. In support of these findings, earlier studies from SSA note the relatively low proportion of infants <24 months of age included.[6, 7] Thus, these findings may not be generalisable to programs across SSA with less extensive coverage of infant diagnosis programs and other resource-related challenges for implementing universal ART.[8-11] Nevertheless, these findings provide evidence of the impact of universal ART practices for reducing mortality in infants through early ART prior to rapid disease progression. It also suggests that the approaches to implementing EID and EIART in South African paediatric HIV programs, relating to linkage to ART initiation after a positive diagnosis, have been successful and can be adapted in similar contexts. Specific approaches include the integration of PMCTCT/EID and infant treatment services and the scale-up of point of care birth HIV testing at delivery for rapid result turnaround time and ART initiation.[2, 10, 12-15] For example, Technau et al. showed a median turnaround time for PCR results of two days at a large maternal and child hospital in South Africa.[14] They also highlighted the need to increase capacity for counselling and outreach focused on the importance of EID while suggesting that counselling could be conducted during antenatal visits to reduce pressure on the staff at delivery.[14]

A somewhat surprising finding was a lack of decline in the median age at ART initiation among children starting ART within five years of age between 2006-2017 across SSA. In contrast, other studies have suggested a decline in age at ART start in children with HIV. However, these studies included children from a broader age range.[5, 6, 16] In contrast, an earlier review found that the age of children initiating was increasing.[7] Our finding may result from the restriction of our study population to children under five years of age at initiation. There are a few explanations for the stable age at ART initiation observed over time in this study. The uptake of universal ART practices in many countries was staggered, and as such, the interpretation of trends in the age of ART start can be complex. Immediate ART eligibility initially applied to the children <2 years in 2010 and furthermore to those <5 years in 2013. Also, there were likely delays in the individual country uptake of the WHO universal ART implementation, which delayed the anticipated impact of the guideline changes on the characteristics of children starting ART.[5] Likewise, the expansion in WHO universal ART initiation criteria have also been accompanied with effective PMTCT (Option B+) since 2013, leading to fewer new infections.[17] Therefore, the median age of ART start reflects the effectiveness of PMTCT in preventing new infections, the capacity for EID and EIART, and the proportion of children who may have been missed in earlier years and present later for treatment. For example, studies in high-income countries show a progressive change in the burden of new paediatric infections to older children, likely due to how effective the PMTCT programmes are at averting new perinatal infections. High-income countries have also shown a substantial decrease in the number of infants with severe immunosuppression, demonstrating substantial improvement in the rate of initiating children on ART before the onset of advanced disease in infants.[18, 19]

Another important finding from this thesis suggests that the paediatric ART guideline revisions since 2008 are associated with a progressive decline in the prevalence of severe disease characteristics at ART among infants and young children in SSA. Specific characteristics assessed were CD4 percent and count, WAZ and WHO disease stage upon treatment initiation among children. A substantial decrease in the prevalence of infants starting ART with WHO stage three or four, or with severe immunosuppression was observed, similar to previous studies.[6, 20-22] Also, between 2006-2017, there was a progressive decline in the proportion of children starting ART while being underweight and having CD4 <15%. However, this thesis showed that approximately half of all children under five years of age and a third of infants within three months of age start ART with advanced HIV disease, similar to earlier studies.[6, [16, 23, 24] Compared to infants, the prevalence of advanced disease markers only declined modestly among those under five years of age at ART start with half still immunosuppressed, underweight and stunted between 2013-2016.

These findings provide additional insights to the existing evidence of the high level of advanced disease among African children initiating ART. [3, 6, 7, 16, 25-28] There are a few factors that explain the persistently high level of advanced HIV disease among young children. As presented in this thesis, the decline in advanced disease characteristics was more substantial among infants initiating ART <3 months of age, the same group with a significant decrease in age at ART start. In contrast, the age at ART start for all children under five remained stable over time, due to possible late diagnosis and treatment initiation after the onset of severe disease. This highlights the importance of early diagnosis and effective linkage to care which is suboptimal in many resource-limited settings.[9, 11, 29].

Additionally, these factors occur within a broader context of structural issues such as limited resources that hinder optimal EID and early infant ART guidelines in resource-limited settings. Further, problems such as shortage of health care workers, poor service integration and limited laboratory services and expertise persist in low-income settings.[30] Furthermore, even in settings with established EID programmes, caregiver dependence remains a significant driver of EIART. Studies show poor return for subsequent EID testing after an initial HIV negative test at birth.[31, 32] Findings support the expansion of immediate ART to all children considering infants who started ART earlier were progressively shown to have a more substantial improvement in CD4%, WHO clinical disease stage, and WAZ over time. However, this thesis indicates the need to focus on context-specific barriers to earlier diagnosis and ART.[33] There is a need to improve the health systems in primary care facilities, promote better counselling services, improve infant PCR testing coverage, and ensure rapid results. In addition, an integrated approach is required, including integration of maternal PMTCT/EID and infant treatment services.

7.1.3 Declining mortality and stable LTFU

Mortality

Across analyses of children starting ART during infancy in South Africa and within five years of age in SSA, mortality declined substantially over time from 2006-2017. The proportion of children who died by 24 months on ART was halved among those who started ART >2013 compared to 2006-2009. Declining mortality is possibly mediated by earlier ART initiation, which reflects the real-world benefit of implementing universal ART for infants. This thesis extends findings on mortality trends among infants starting ART by providing data on mortality in the first three months of life.[16, 24, 34] Nevertheless, despite the improvement in survival, mortality levels remained stagnated between 2010-2016 among infants and older children. This is a trend that has also been suggested in adult studies. There are a few explanations of underlying factors outside of ART effectiveness that may be contributing to the persistent level of mortality observed. In the more recent context of widespread effective PMTCT programmes and declining new perinatal HIV infections, there has been an increase in the subset of high-risk women living with HIV who are more vulnerable to HIV transmission. In the ART era, women who acquire HIV during pregnancy increasingly contribute disproportionately to new paediatric infections.[35] Additionally, mothers who acquire HIV late in pregnancy, particularly in the era of Option B+, are more likely to have characteristics such as high viral loads, poor retention in care and reduced adherence, which would increase the risk of transmission to their infants.[36]

This timing of infant HIV acquisition from the mother (in utero, intrapartum or postnatally via breastfeeding) affects subsequent infant mortality risk, and so the relative proportion of infants acquiring HIV in each of these time periods will impact overall mortality estimates. In-utero HIV acquisition, is associated with higher mortality compared to acquisition intrapartum or via breastfeeding.[37-40] A study revealed that 24% of in utero-infected infants either died or were lost to follow-up by six months of age.[39] In contrast HIV acquisition during breastfeeding is associated with lower mortality than intrapartum transmission. With wide coverage of effective PMTCT for all women with HIV diagnosed antenatally, a greater proportion of the small number of infants that still acquire HIV will be infected in utero or postnatally, whereas in the absence of PMTCT most transmission occurred intrapartum. The nett effect of this shift in timing of HIV acquisition to favour groups with both higher (in utero transmission) and lower (postnatal transmission) mortality risk than the previous predominant intrapartum transmission, may be that mortality remains relatively stable. Furthermore, we also hypothesise that with the expansion of universal ART, the stable mortality rate after 2010 observed in this analysis could be due to the inclusion of an increasing population of vulnerable infants initiating ART, who might otherwise have died in the period prior to expansion of WHO ART eligibility criteria. Also, in the infants and children who acquire HIV despite good coverage of effective PMTCT programmes, may be from more socioeconomically disadvantaged backgrounds, which adversely affects care engagement and adherence to medication for both mothers and infants. Therefore, there is a need for targeted interventions to support nutrition and ART adherence in children living with HIV.[22, 36]

A further contribution to the stable mortality rates in children on ART is that HIV disease progression may be hastened among children in Africa due to the excess burden of disease and underlying conditions. One study reported that >40% of children in LMICs started ART with severe immunodeficiency compared to <20% in high-income settings.[21] For example, high prevalence of tuberculosis, bacterial coinfections and malnutrition may facilitate rapid disease progression and hinder optimal ART outcomes in children in resource-limited settings.[22, 27, 41, 42]

Another critical finding this thesis presents is the evidence of substantial variation in paediatric survival on ART across SSA and World Bank country income groups. These variations are likely due to socioeconomic inequalities resulting in poor access to ART and structural factors resulting in poor uptake of EID. Therefore, more effort is required to achieve the sustainable development goal which aims at reducing inequality within and among countries (Goal 10). Variations also existed across geographic locations in SSA. Like reports from other studies, West Africa had the highest mortality burden among children living with HIV.[26] Socioeconomic inequalities could also be supported by our finding of WAZ as a predictor of mortality, especially for children starting ART between 3-5 years. This suggests that malnutrition could be an underlying risk factor driving ongoing mortality in this region. A study revealed that children underweight at ART initiation with poor adherence to ART had a higher risk of mortality.[39]

Together, these findings draw attention to the lack of generalizability of paediatric ART outcomes and their determinants across SSA. Therefore, it is essential not to apply a 'one-size-fits-all' approach to interventions to monitor treatment effectiveness and improve survival of children living with and affected by HIV.

Loss to follow-up

Declining advanced disease at ART initiation will only result in treatment outcomes if children are retained in care and closely monitored. However, this thesis suggests that LTFU has remained unchanged between 2006-2017 among young children starting ART under five years of age and is a challenge that continues to undermine the success of ongoing paediatric ART interventions. This analysis found that high early LTFU following the first three months of ART remained consistent across guideline periods. Studies show that the early postpartum period of the HIV care cascade for women is characterised by high rates of LTFU among mothers.[32, 43, 44] It is also important to note that due to universal ART practices, it is likely that LTFU occurring prior to ART start has been shifted to LTFU on treatment. Supporting this hypothesis, we found that >70% of infants LTFU after ART initiation within three months of age were lost after ART initiation date and did not return. Also, adult studies show that early or same-day ART initiation is not associated with an increase in patient attrition.[68] In addition, several studies of infants with HIV have demonstrated a high level of LTFU before linkage to care for ART initiation.[12, 32, 40, 43-46]

Given the uptake of earlier diagnosis including birth HIV testing and the increased level of transmission among mothers who acquire HIV during pregnancy, this high level of LTFU shortly after diagnosis could also be attributed to the psychosocial factors arising from the burden of multiple HIV positive diagnoses. A case-control study conducted in Botswana and including 313 children, demonstrated that caregivers of those LTFU were more likely to be dealing with psychosocial issues such as stigma and disclosure of HIV status compared to controls who were retained in care.[32] Challenges such as stigma and limited support systems in place make caregivers less likely to return to the clinics after initial diagnosis. Therefore, it is critical to focus on finding innovative solutions to address the psychosocial and socioeconomic challenges among women and caregivers with HIV.

Furthermore, many studies indicate an increase in the level of LTFU among children following the implementation of universal ART.[47-51] It has been suggested that rapid decentralisation of HIV services combined with an increased patient burden in an under-resourced health system are significant factors contributing to high LTFU. Another factor enumerated is the poor documentation of patient transfers and mobility among mothers. Another factor enumerated is the poor documentation of patient transfers/referrals which may falsely elevate the number of children appearing LTFU but who have actually transferred. This could be addressed by improving the recording of patient transfers. Further, mobility among mothers may lead to them self-transferring their infants to receive treatment at a different facility (so-called “silent transfers”). Linkage of data across different facilities is thus needed to accurately assess LTFU at the program level. Given the vulnerability of infants with HIV to early mortality on ART, there may be a high level of unascertained mortality classified as LTFU. Studies show that an estimated 10-40% of children documented as LTFU by ART programmes had died.[34, 52, 53] Therefore, there is a need to intensify the tracing of outcomes among infants and children classified as LTFU to estimate mortality trends accurately.

7.1.4 Suboptimal viral suppression

Sustained virologic suppression is the primary measure of treatment success. The UNAIDS 90:90:90 target promotes efforts towards achieving undetectable HIV viral load in 90% of patients on ART. In South Africa, an increasing number of infants are getting diagnosed and initiated on ART as early as birth. Also, ART initiation in neonates and infants is complex, with limited regimen options available. Therefore, this thesis focused on assessing viral suppression in infants.

Similar to other findings among older children, suboptimal viral suppression (<400 copies/ml) was observed with suppression at six months achieved by only about half of infants starting ART aged <3 months. [16, 54, 55] Infants have been shown to suppress slowly on ART compared to older children.[56] However, findings from this work extend existing evidence by demonstrating a trend suggesting poorer viral suppression over time in infants despite early infant ART, higher CD4% and lower VL at ART start. Infants starting ART with a viral load of >1 million copies/ml had an increased risk of virological non-suppression by six months on ART.

Furthermore, considering the high uptake of effective PMTCT and infant prophylaxis regimens, increasing resistance levels remains a plausible explanation for worsening viral suppression levels. [57] One of the key factors associated with poorer viral suppression over time centres around suboptimal treatment: limited availability of antiretrovirals for use in the neonatal period, frequent need for changing doses due to weight change and palatability-related issues of the available drugs. These factors could lead to under-dosage and decreased bioavailability. Also, more than half of infants in this study were initiated on an abacavir-based regimen after the guideline recommended a change from stavudine-based regimen in 2010. Studies have described lower virological effectiveness of abacavir-containing regimens compared to zidovudine, stavudine or a protease inhibitor-based (PI) regimen. [5, 16, 55, 58, 59]

Nevertheless, further analysis shows promising findings of long-term virologic suppression among infants retained in care. In Chapter 6, this thesis presents virological outcomes up to five years on ART among infants starting ART before one year of age. Findings show that 70% of children were suppressed by five years on ART. Similar findings of good viral suppression rates have been presented in a randomised control trial study and from high-income settings. [18, 60-64] This finding highlights that immediate ART among infants has long-term benefits for children initiating ART in the context of routine care during infancy in RLS. Nevertheless, infants starting ART before three months of age were less likely to be virologically suppressed at all time points on ART (1, 3 and 5 years) than those who started ART at 4-7 and 8-12 months of age. These findings re-emphasise the difficulty of neonatal ART in RLS, as highlighted earlier. [12, 65-67] Young infants initiated on ART require specific attention and closer monitoring. Furthermore, we found that severe disease characteristics at ART initiation (CD4% <15 and WAZ <-2) were associated with failure to suppress in the long-term, demonstrating that early ART initiation remains critical for optimal long-term outcomes.

7.2 Limitations and strengths

The analyses presented in this thesis are not without limitations. Within each result chapter (3-6), specific strengths and limitations have been presented in the individual discussion section. Therefore, this section presents strengths and limitations underpinning this thesis as a single body of work. It is important to note that causality cannot be assumed due to the retrospective cohort study design of the analyses; therefore, the predictors identified need to be interpreted with caution. Also, based on the entry point of ART initiation for our study population, a vulnerable group of children who are more likely to die before linkage to care are likely to have been excluded. Therefore, mortality and LTFU levels are likely to be higher than estimated in this research.

Furthermore, consistent with the challenges of utilizing routine data, approximately 25-40% of children had missing data on ART initiation characteristics, particularly CD4 percentages, viral load and anthropometry measures. In addition, crucial data on maternal characteristics were unavailable. This limitation was accounted for by utilising multiple imputation methods to impute missing baseline variables across analysis. In addition, subgroup analyses were conducted to validate findings in cases of potential bias due to mortality under ascertainment and varying patient follow-up duration. There are also multiple social and psychological aspects associated with HIV diagnosis. Additional support is needed when trying to successfully navigate treatment of self and one’s infant especially for women in RLS. These critical aspects were beyond the scope of the data for this thesis but are nonetheless very important in settings plagued by high levels of poverty and inequality as well as social conflict in some countries.

Notwithstanding these limitations, this thesis has several strengths. This thesis presents findings from one of the largest observational cohort of young children living with HIV in SSA. For example, analyses in Chapter 3 include >32 000 children from sub-Saharan Africa, providing a robust assessment of the impact of ART guidelines changes over time on the health outcomes of children and infants with HIV. Also, the effect of bias due to under-ascertainment of mortality was considered by recalculating mortality with respect to different assumptions of mortality levels among children classified as LTFU. All results presented included a cohort of children staring ART during various periods of the rollout of universal ART for infants <12 months in 2008, <2 years in 2010 and all children <5 years of age in 2013. In the cohort of children in SSA, approximately 20% of children started ART after 2013, in the era of expanded access to PMTCT. The cohort of infants included in chapter 4-6 provides novel insights into the progress towards earlier infant ART initiation and the effectiveness of early infant ART in South Africa. EID uptake across SSA is slow; hence data on early-treated infants in resource-limited settings are scarce. Therefore, this thesis presents timely valuable information for use in other settings across SSA.

7.3 Recommendations for future research and policy

The findings presented in this thesis have led to identifying areas for future research and policy improvement. Understanding the factors driving inequalities in outcomes among CLHIV in the era of widespread ART, particularly between LICs and LMICs, warrants further investigation. There is a need to focus on context-appropriate improvements in health systems, service delivery and patient support in various settings across RLS. Furthermore, to design effective services to maximise the health of perinatally infected children, there is a need to consider the underlying factors contributing to persistent mortality carefully. Given the declining new paediatric infections, high coverage of PMTCT and a narrowing of the paediatric HIV population to a high-risk subset, maternal characteristics which may be driving the persistent mortality come to the fore. These include challenges for mothers maintaining their own and their infants' adherence and addressing the psychosocial burden of living with HIV which impacts on the outcomes of infants and young children with HIV. It is important to urgently address the specific challenges facing mothers of infants with HIV, and also to explore emerging factors associated with poor outcomes in the universal ART era. [39] For example, there is a need to identify and consider mothers and caregivers' socioeconomic and mental health needs as EID and ART initiation may be inadequate to improve child outcomes. Adequate maternal counselling and psychosocial support during antenatal care are essential. It is vital that counselling includes a comprehensive description of EID and infant ART. This support is crucial and is recommended throughout the various stages of the HIV care cascade. Therefore, there is a need for future research to focus on identifying maternal-related risk factors that may influence child ART outcomes in order to inform effective maternal/caregiver-related interventions and support. It is becoming increasingly evident that programmes need to focus on tailored approaches to support women living with HIV, and to reduce the incidence of new HIV infections in girls and young women, especially during pregnancy and breastfeeding.

Since the age at ART initiation among young children in SSA did not significantly decline over time, it is important to focus on scaling up early diagnosis and treatment. Research needs to focus on the barriers to implementing EID, specifically around program linkage in RLS. Studies show the need for a context-based approach to implementing universal ART policies, as settings within SSA vary widely. For example, the coverage of EID is 62% in Southern Africa compared to 26% in West Africa. [17] EID is challenging in RLS, particularly in rural settings with limited access to laboratory facilities as diagnostic tests for infants that rely on HIV DNA or RNA detection assays should be utilized instead of serologic assays used in older children. Additional costs related to universal ART implementation include the need for reliable viral testing for EID and viral load monitoring to effectively monitor responses to ART such as treatment failure and virologic resistance, especially in infants with prior PMTCT exposure.

Similarly, there is a need for improvement of documentation of patient transfers and better linkage between facilities. Further research is needed to assess the outcome of those LTFU. Studies reveal that the majority of children LTFU may actually be deceased. [24, 34, 52] It is essential to focus on tracing studies to determine the true outcomes of those LTFU in the context of expanded access to ART where many children are starting ART earlier with less advanced disease and are less likely to die.

An increasing proportion of children are now surviving and living longer on lifelong ART. However, optimal viral suppression and retention in care are needed to achieve the benefits of earlier HIV diagnosis and immediate ART initiation. Efforts such as the introduction of newer regimens such as dolutegravir which has been shown to be more effective in achieving viral suppression and preventing development of resistance. In addition, the feasibility of strategies improving tracking of patients by the facility and linkage to care by utilising the services of community health workers and other innovative digital health strategies need to be assessed in various settings.

Finally, although this thesis shows in Chapter 4 that good long-term virologic outcomes can be achieved in resource-limited settings, data on long-term outcomes are scarce, especially among early-treated infants in SSA. There is a need to continue to monitor the long-term outcomes of children initiating immediate ART during infancy, including long-term viral suppression, chronic conditions and comorbidities, early childhood development and successful integration into normal school education. It is important to focus on optimising the quality of life (the so-called "4th 90") to ensure that children are not only surviving but have improved quality of life.

7.4 Conclusion

This thesis demonstrated a trend towards earlier ART initiation, improved health status at ART initiation and decreasing mortality among infants and young children with HIV in SSA, in the context of expanding ART initiation guidelines from 2006-2016. Nevertheless, mortality plateaued after 2010, and there was no substantial improvement in short-term viral suppression and program retention over time. Further highlighted is the need to address the inequities that predispose women to HIV acquisition and poor access or engagement to care. These findings indicate that factors beyond ART effectiveness may be driving poor outcomes despite widespread ART for prevention and treatment of paediatric HIV. As increasing numbers of children are initiated on treatment at younger ages, improved access to viral load monitoring and caregiver support will become more critical. Therefore, there is a need for support for an increasing population of vulnerable mother-infant pairs who initiate immediate ART in the context of universal ART practices but who would otherwise have been LTFU or died before program linkage and ART initiation in the pre-universal ART era. Specific support such as EID counselling, psychosocial support, and community outreach at each step of the care cascade is recommended. Furthermore, findings also show a worsening of virological outcomes in infants starting ART <3 months of age over time as widespread access to PMTCT, EID and early infant ART expands. This finding highlights a need to focus on increased monitoring of viral load and treatment resistance among infants. There is also a need to provide adherence support for mothers and ensure the availability of effective and easy to administer neonatal and infant ART regimens. Another significant contribution of this thesis is the demonstration of good long-term outcomes of early infant ART.

In conclusion, this thesis provides a unique opportunity to understand the program-level effect of expanded access to paediatric ART, using data from large cohorts of infants and young children living with HIV from several countries in SSA. It shows that prompt identification of children with HIV and early treatment initiation is essential but insufficient for improving survival and ensuring optimal program retention and viral suppression. This is increasingly important as the focus in paediatric HIV programs have shifted to PMTCT and health outcomes of a larger and equally important population of HIV-affected children. This shift presents a risk of decreased resource allocation at a program level towards improving the outcomes of the few children who still acquire HIV in the current ART era. Therefore, a holistic and individualised approach to optimising the survival and related outcome of children living with HIV is recommended. Integrated HIV service delivery services that support interventions including nutrition, psychosocial support, child development, counselling and adherence support, are needed. Furthermore, it is important to urgently monitor and understand the long-term paediatric ART outcomes in the context of immediate lifelong ART, with a focus on infants starting ART within three months of age.

7.5 References

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Chapter 8: Appendices

8.1 Supplementary material for Chapters 3-4

8.1.1 Chapter 3

Table 8.1 Characteristics and outcomes of children starting antiretroviral therapy at ≤5 years of age in sub-Saharan Africa by country income group

Characteristics	Total (N= 32,221)	Low income (N= 11,510)	Lower-middle income (N= 8252)	Upper-middle income (N= 12,459)	*P*
Region					
Central Africa	707 (2.2)	403 (5.7)	304 (2.3)	0 (0)	<0.001
East Africa	5044 (15.7)	840 (12.0)	4204 (32.9)	0 (0)	
Southern Africa	24,410 (75.8)	4825 (68.9)	7126 (55.8)	12,459 (100.0)	
West Africa	2060 (6.39)	934 (13.3)	1126 (8.8)	0 (0)	
Sex					
Female	16,1015 (49.1)	5687 (49.4)	4109 (49.8)	6324 (50.8)	0.100
Male	16,120 (50.0)	5828 (50.6)	4143 (50.2)	6135 (49.2)	
Median age in months (IQR)	20.4 (8.3-34.8)	24.2 (13.5-39.1)	22.6 (13.3-37.5)	13.2 (4.7-26.8)	<0.001
Age category in months					
0-3	2207 (6.8)	346 (3.0)	182 (2.2)	1679 (13.5)	
4-12	7933 (24.6)	2154 (18.7)	1550 (18.7)	4229 (33.9)	<0.001
13-36	14,505 (45.0)	5599 (48.6)	4303 (52.1)	4603 (36.9)	
37-60	7576 (23.5)	3411 (29.6)	2217 (26.9)	1948 (15.6)	
Median CD4 percentage (IQR)	17 (11-24)	15 (10-21)	16 (11-23)	18 (12-26)	<0.001
Median CD4 count (cells/µl) (IQR)	708 (380-1181)	706 (398-1149)	724 (420-1142)	695 (331-1245)	0.145
Severely immunosuppressed					
No	6096 (34.3)	1993 (42.8)	1609 (33.2)	2494 (30.2)	<0.001
Yes	11,680 (65.7)	2662 (57.2)	3243 (66.8)	5775 (69.8)	
Missing	14,445	6855	3400	4190	
Median WAZ (IQR)	-1.8 (-3.2 to -0.7)	-2.1 (-3.4 to -0.9)	-.1.9 (-3.2 to -0.6)	-1.9 (-3.2 to -0.7)	<0.014
WAZ category					
≤-3	6839 (28.6)	3084 (28.3)	1894 (28.7)	1861 (29.0)	0.094
>-3 to ≤-2	4514 (18.8)	1993 (18.3)	1275 (19.3)	1246 (19.4)	
>-2	12,548 (52.4)	5821 (53.4)	3422 (51.9)	3303 (51.5)	
Missing	8329	612	1661	6049	
Median HAZ (IQR)	-2.5 (-3.8 to -1.3)	-2.6 (-3.8 to -1.2)	-2.7 (-4.0 to -1.3)	-2.4 (-3.5 to -1.2)	<0.001
HAZ category					
≤-3	7470 (40.8)	3561 (41.5)	2318 (44.6)	1685 (36.0)	<0.001
>-3 to ≤-2	3902 (21.3)	1778 (20.7)	1042 (20.0)	1106 (23.7)	
>-2	6917 (37.8)	3250 (37.8)	1838 (35.4)	1884 (40.3)	
Missing	13941	2921	3054	7784	
Outcome					
Retained	20,160 (62.6)	7169 (62.3)	4978 (60.3)	8013 (64.3)	<0.001
Death	1654 (5.1)	677 (5.8)	557 (6.8)	420 (3.4)	
LTFU	7,441 (23.0)	2795 (24.3)	2627 (31.8)	2019 (16.2)	
TFO	2966 (9.2)	869 (7.5)	90 (1.2)	2007 (16.1)	

HAZ: Height-for-age Z score; IQR: Interquartile range; LTFU: Loss to follow-up; TFO: Transfer out; WAZ: Weight-for-age-Z-score; interquartile range Chi-squared test used for categorical variables and Kruskal-Wallis test used for continuous variables

Table 8.2 Cumulative incidence and 95% confidence intervals of 24-month outcomes (mortality, loss to follow-up, and transfer out) by ART initiation year, country income group, and geographic region

	N	Mortality % (95% CI)	LTFU % (95% CI)	Transfer out % (95% CI)
Total cohort	32,219	5.1 (4.8-5.3)	20.5 (20.1-21.0)	9.2 (8.8-9.5)
ART initiation cohort				
2006-2010	14,943	6.4 (6.1-6.8)	17.7 (17.1-18.3)	9.3 (8.9-0.9)
2011-2013	9988	4.6 (4.2-5.1)	24.5 (23.7-25.4)	10.8 (10.2-11.5)
2014-2017	7290	2.9 (2.5-4.3)	21.0 (20.1-21.9)	6.5 (6.0-7.1)
Region				
East Africa	5044	6.7 (6.0-7.4)	21.6 (20.5-22.8)	5.6 (5.0-6.3)
West Africa	2060	10.6 (9.3-12.0)	16.7 (15.1-18.3)	6.0 (5.0-7.1)
Central Africa	707	2.9 (1.8-4.4)	18.2 (15.8-21.6)	0
Southern Africa	24,410	4.3 (4.1-4.6)	20.7 (20.2-21.2)	10.4 (10.0-10.8)
Country income group				
Low income	11,510	5.8 (5.4-6.3)	21.5 (20.8-22.3)	7.5 (7.0-8.0)
Lower-middle income	8252	6.7(6.2-7.2)	28.6 (27.6-29.5)	1.0 (0.8-1.3)
Upper-middle income	12, 459	3.3 (3.0-3.6)	14.3 (13.7-15.0)	16.1(15.4-16.7)

Table 8.3 Complete case analysis for hazard ratios of mortality (and 95% confidence intervals) among children starting ART at <5 years of age in sub-Saharan Africa (N=13,311).

		Model I	Model II	Model III
Characteristic	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**
ART initiation year				
2006-2010	1	1	1	1
2011-2013	0.74 (0.66-0.83)	0.77 (0.65-0.90)	0.82 (0.69-0.96)	0.78 (0.66-0.92)
2014-2017	0.52 (0.45-0.61)	0.66 (0.51-0.85)	0.73 (0.56-0.93)	0.65 (0.51-0.84)
Country income group				
Low income	1	1	-	1
Lower-middle income	1.16 (1.03-1.31)	1.00 (0.84-1.20)	-	1.01 (0.83-1.24)
Upper-middle income	0.56 (0.49-0.65	0.40 (0.32-0.49)	-	0.40 (0.31-0.52)
Region				
East Africa	1	-	1	1
West Africa	1.67 (1.41-1.98)	-	1.58 (1.25-1.99)	1.52 (1.18-1.94)
Central Africa	0.40 (0.25-0.62)	-	0.52 (0.29-0.94)	0.54 (0.29-0.99)
Southern Africa	0.67 (0.60-0.76)	-	0.81 (0.67-0.99)	1.17 (0.96-1.42)
Age at ART start (months)				
0-3	1	1	1	1
4-12	1.15 (0.95-1.39)	0.67 (0.51-0.88)	0.87 (0.66-1.13)	0.67 (0.51-0.88)
13-36	0.70 (0.58-0.85)	0.33 (0.25-0.44)	0.55 (0.42-0.72)	0.34 (0.25-0.45)
37-60	0.37 (0.30-0.46)	0.22 (0.16-0.30)	0.38 (0.28-0.52)	0.23 (0.26-0.41)
Female	0.91 (0.83-1.00)	0.97 (0.85-1.11)	0.96 (0.85-1.11)	0.97 (0.83-1.00)
Severely immunosuppressed				
No	1	1	1	1
Yes	2.74 (2.32-3.23	1.96 (1.63-2.36)	1.87 (1.56-2.25)	1.93 (1.61-2.32)
WAZ				
≥-2	1	1	1	1
< -2 - ≥-3	1.78 (1.52-2.09)	1.63 (1.33-2.01)	1.58 (1.29-1.95)	1.63 (1.33-2.01)
<-3	4.22 (3.74-4.76)	3.51 (3.00-4.12)	3.35 (2.86-3.93)	3.44 (2.93-4.03)

Model I: Model adjusted for country income group, Model II: Model adjusted for geographic region, Model III: Model adjusted for both country income group and geographic region. CI: confidence interval, HR: Hazard ratio; WAZ: Weight-for-age Z-score

Table 8.4 Complete case analysis for hazard ratios of mortality (and 95% confidence intervals) stratified by age at ART initiation (N=13,311)

	<12 months	**13-36 Months**	**37-60 Months**
Characteristic	adjusted HR (95% CI) N=3941	adjusted HR (95% CI) N=5925	adjusted HR (95% CI) N= 3445
ART initiation year			
2006-2010	1	1	1
2011-2013	0.85 (0.66-1.09)	0.74 (0.57-9.5)	0.67 (0.43-1.05)
2014-2017	0.52 (0.34-0.80)	0.85 (0.61-1.20)	0.58 (0.27-1.21)
Country income group			
Low income	1	1	1
Lower-middle income	0.92 (0.65-1.31)	0.98 (0.75-1.29)	1.30 (0.79-2.11)
Upper-middle income	0.41 (0.28-060)	0.39 (0.26-0.58)	0.86 (0.40-1.85)
Region			
East Africa	1	1	1
West Africa	1.50 (0.97-2.33)	1.35 (0.94-1.93)	2.19 (1.28-3.77)
Central Africa	0.26 (0.03-1.98)	0.50 (0.22-1.14)	0.95 (0.31-2.91)
Southern Africa	1.11 (0.76-1.62)	1.24 (0.94-1.64)	0.89 (0.56-1.40)
Female	1.12 (0.91-1.38)	0.93 (0.76-1.15)	0.67 (0.46-0.97)
Severely immunosuppressed			
No	1	1	1
Yes	1.97 (1.41-2.75)	1.83 (1.41-2.38)	1.95 (1.31-2.90)
WAZ			
≥-2	1	1	1
< -2 - ≥-3	1.37 (0.99-1.90)	1.74 (1.25-2.42)	2.43 (1.48-3.99)
<-3	2.53 (1.99-3.20)	4.32 (3.34-5.58)	5.09 (3.32-7.81)

HR: Hazard Ratio, CI: 95% Confidence interval; IQR: Interquartile range; WAZ: Weight-for-age-Z-score;

Table 8.5 Cumulative incidence (95% confidence intervals) of mortality under varying assumptions of proportion of death among those lost to follow up (LTFU)

	Proportion of assumed death among LTFU			
	10%	**30%**	**50%**	**100%**
Overall	7.0 (6.9-7.0)	11.3 (10.9-11.6)	15.4 (15.0-15.8)	25.7 (25.2-26.2)
Year of ART start				
2006-2009	8.2 (7.8-8.7)	15.3 (14.7-15.8)	12.5 (12.0-13.0)	24.2 (23.5-24.8)
2011-2013	7.0 (6.5-7.5)	11.9 (11.2-12.5)	17.3 (16.5-18.0)	29.2 (28.3-30.1)
2014-2017	5.1 (4.6-5.6)	9.4 (8.8-10.1)	13.1 (12.4-13.9)	23.9 (22.9-24.9)
Country Income Group				
Low income	7.7 (7.3-8.2)	12.0 (11.4-12.6)	15.7 (14.8-16.5)	27.4 (26.6-28.2)
Lower-middle income	9.8 (9.2-10.5)	15.6 (14.8-16.4)	20.0 (19.3-20.7)	35.3 (34.3-36.3)
Upper-middle income	4.8 (4.4-5.2)	7.7 (7.3-8.2)	10.6 (10.1-11.2)	17.7 (17.0-18.4)

8.1.2 Chapter 4

Table 8.6 Cumulative incidence (95% CI) of mortality and loss to follow-up by 6 months on ART

Year of ART start	Mortality*	LTFU**
Overall	5.0% (4.1, 6.2)	20.8% (18.9, 22.8)
2006-2009	8.0% (5.8, 10.7)	22.9% (19.3, 26.8)
2010-2012	4.1% (2.6, 6.1)	19.5% (16.2, 22.9)
2013-2017	3.6% (2.4, 5.2)	20.4% (17.4, 23.5)

*Estimates accounting for LTFU and TFO as competing risks; **Estimates of LTFU occurring before mortality and TFO.

Table 8.7 Factors associated with no follow-up and LTFU after a subsequent visit on ART using imputed dataset (n=1692)

	No follow-up		Lost after subsequent visit	
	Crude	Adjusted	Crude	Adjusted
Age in weeks	0.98 (0.75-1.28	0.96 (0.70-1.31)	0.80 (0.52-1.24)	0.79 (0.47-1.33)
Female	0.91 (0.71-1.17)	0.91 (0.71-1.17)	0.82 (0.54-1.23)	0.80 (0.53-1.21)
ART initiation year				
2006-2009	Ref			
2010-2012	0.78 (0.57-1.06)	0.50 (0.35-0.70)	0.76 (0.43-1.35)	0.68 (0.36-1.29)
2013-2017	0.69 (0.51-0.92)	0.36 (0.25-0.51)	1.20 (0.73-1.96)	0.91 (0.47-1.75)
WHO disease stage				
I/II	Ref			
III/IV	0.89 (0.67-1.18)	0.95 (0.68-1.34)	0.80 (0.46-1.41)	0.84 (0.42-1.66)
CD4 percentage	0.99 (0.98-1.00)	1.00 (0.99-1.01)	1.00 (0.98-1.01)	0.99 (0.98-1.01)
WAZ				
>-2	Ref			
≤-2	0.94 (0.65-1.34)	0.97 (0.68-1.39)	0.91 (0.54-1.53)	0.91 (0.53-1.56)
Log viral load	0.97 (0.85-1.11	1.01 (0.89-1.15)	1.2 (0.79-1.98)	1.06 (0.80-1.45)
PMTCT exposure				
No	Ref			
Yes	0.49 (0.35-0.67)	0.93 (0.56-1.54)	0.88 (0.57-1.36)	0.87 (0.47-1.58)
Unknown	0.99 (0.72-1.35)	2.4 (1.32-4.59)	0.38 (0.17-0.83)	1.02 (0.32-3.21)

CI, confidence interval; HR, hazard ratio; WAZ, weight-for-age z-score; WHO
*Status of infant exposure to maternal or infant PMTCT

Table 8.8 Factors associated with mortality and loss to follow-up: complete case analysis (n=439)

	Mortality		**Loss to follow-up**	
	Crude HR (95% CI)	**Adjusted HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
Age in weeks	1.47 (0.89-2.45)	1.06 (0.41-2.75)	0.93 (0.74-1.17)	0.90 (0.30-2.67)
Female	0.68 (0.44-1.02)	0.80 (0.44-1.45)	0.89 (0.72-1.09)	0.39 (0.18-0.81)
ART initiation year				
2006-2009	Ref			
2010-2012	0.47 (0.27-0.79)	0.63 (0.28-1.40)	0.77 (0.59-1.01)	0.50 (0.19-1.30)
2013-2016	0.46 (0.28-0.75)	0.85 (0.35-2.06)	0.80 (0.62-1.03)	1.23 (0.44-3.74)
WHO disease stage				
I/II	Ref			
III/IV	2.05 (1.23-3.40)	1.01 (0.47-2.15)	0.67 (0.51-0.88)	1.19 (0.47-2.99)
CD4 percentage		0.98 (0.96-1.01)		1.01 (0.98-1.03)
WAZ				
>-2	Ref			
≤-2	2.6 (1.48-4.60)	1.89 (0.84-3.90)	0.92 (0.59-1.43)	0.44 (0.20-0.97)
Log viral load	1.24 (0.99-1.55)	1.09 (0.75-1.59)	1.03 (0.88-1.22)	1.19 (0.82-1.73)
PMTCT exposure*				
No	Ref			
Yes	1.17 (0.74-1.85)	1.17 (0.59-2.32)	0.59 (0.46-0.77)	0.63 (0.26-1.54)
Unknown	1.10 (0.62-1.97)	2.28 (0.79-6.43)	0.83 (0.62-1.11)	2.16 (0.0-1.00)

CI, confidence interval; HR, hazard ratio; WAZ, weight-for-age z-score; WHO
*Status of infant exposure to maternal or infant PMTCT