



National University of Ireland, Galway  
*Ollscoil na hÉireann, Gaillimh*

# **Social and clinical features of HIV infection in older children and adolescents in Zimbabwe**

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I, Grace McHugh, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

**My role:**

I served as study physician for the duration of the study. I designed and wrote the standard operating procedures for clinical aspects of the study. I oversaw all the data collection by nursing staff and visited each clinical site weekly, often times more frequently. I trained the nursing staff on initiation and management of antiretroviral treatment in children and adolescents. I cleaned the data collected after initial review by data team. I designed and conducted the analysis for each study outcome. I provided further training for the nursing staff in the employ of the clinics on care and management of children and adolescents living with HIV to ensure ease of transfer of care of children once the study had reached an end. I wrote the first drafts of submitted manuscripts for publication based on research findings and circulated amongst co-authors, whose edits and comments were then incorporated into the final drafts for submission to journals for publication. I served as the corresponding author on my paper submissions to journals and was responsible for rebuttal of editorial comments.

## Acronyms

ART	Anti-Retroviral Therapy
CD4	CD4+ lymphocyte
EID	Early infant diagnosis
FEV1	Forced Expiratory Volume at one second
FVC	Forced Vital Capacity
HIV	Human Immunodeficiency Virus
HRCT	High resolution computed tomography
HTLV-3	Human T-Cell leukaemia virus
IQR	Interquartile range
LTFU	Lost to follow up
MTCT	Mother to child transmission
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PHC	Primary Health Care Clinic
PITC	Provider Initiated Testing and Counselling
PLHIV	People living with HIV
PMTCT	Prevention of Mother to Child Transmission
SdNVP	Single dose Nevirapine
SSA	Sub-Saharan Africa
TB	Tuberculosis
VL	Viral load
WHO	World Health Organization

## **Abstract**

### ***Introduction***

HIV infection has had a devastating effect on morbidity and mortality of children and adolescents, particularly in low- income settings. Zimbabwe has been at the epicentre of the HIV epidemic since mid-1990. This study serves to describe the clinical and sociodemographic features of children aged 6-15 years at time of HIV diagnosis and describe their clinical outcomes at 18 months post diagnosis.

### ***Methods***

A prospective cohort study was performed from January 2013-June 2016 in seven primary care clinics in Harare, Zimbabwe. Children found to be newly diagnosed with HIV were offered enrolment and HIV treatment as per national guidelines. Their clinical events and outcomes over the course of 18 month follow up were documented.

### ***Results***

In total, 385 children were enrolled. The median age was 11 years (interquartile range 8-13). Median CD4 count at diagnosis was 375 cells/mm<sup>3</sup>. 95% had acquired HIV perinatally. A high proportion of chronic illness was noted at time of diagnosis particularly respiratory tract illness. Disclosure of their HIV status to children by their caregiver at time of diagnosis was low. Although a low hospitalisation and mortality was noted at 18 months, virological outcomes were poor with only two- thirds of children achieving virological suppression one year post antiretroviral therapy commencement.

### ***Conclusion***

HIV testing strategies need to be improved for older children to ensure earlier identification of infection and so treatment can be initiated before onset of chronic illness. Methods to support caregivers and healthcare providers to

discuss HIV with children need to be enhanced in Zimbabwe's national HIV program. Adherence to treatment is a challenge in this age group that needs to be urgently addressed as we move towards an AIDS free generation.

## **1. Introduction**

### **1.1 Background**

Since the first description of Acquired Immune Deficiency Syndrome (AIDS) and recognition of the causal Human Immune Deficiency Virus (HIV) in the early 1980s, over 39 million children and adults have died globally of the disease (1). Concerted global efforts to roll-out anti-retroviral therapy (ART) in regions most in need has seen HIV-associated mortality declining, with a 45% decrease from the peak of AIDS-related deaths in 2005 to 2015 (2).

In addition, use of ART to prevent mother-to-child transmission has resulted in a decrease by 51%, since 2010, in the number of new HIV infections amongst children under 15 years old (3). HIV-infected infants are at high risk of rapid disease progression with mortality of 35% by the first year of life and cumulative mortality of 50% by the end of 2<sup>nd</sup> year of life observed in cohorts in the pre-ART era (4).

Over the past decade, increasing numbers of older children and adolescents have been presenting to health services with previously undiagnosed perinatally-acquired HIV (5). These children were infected when interventions to prevent mother to child transmission (PMTCT) were not widely available. This group of children have much slower disease progression and it is now recognised that at least a third of infants with HIV are “slow-progressors” with a median survival of at least 16 years without treatment. The recognition that a relatively large proportion of children experience slower disease progression occurred only as HIV epidemics matured: given the high mortality observed among untreated infants in the pre-ART era, it had been assumed that survival beyond early childhood would be exceptional.

A consequence of this is that until recently, older children have received much less attention by HIV programmes than infants and younger children, for example HIV diagnosis among older children often only occurs after presentation with advanced HIV disease with initiation of ART when children are already severely

immunocompromised, reducing the chances of successful treatment outcomes (6).

Given the risk of rapid disease progression in HIV-infected infants, World Health Organisation (WHO) guidelines have recommended immediate initiation of ART, upon a diagnosis of HIV being made, in infants, since 2010, and subsequently in children aged 2-5 years. This was based on findings of the landmark CHER trial which showed a 76% reduction in early infant mortality if ART was commenced soon after diagnosis (7,8). Such evidence is lacking for older children and in 2013, children over 5 years of age followed adult WHO guidelines for ART initiation of a CD4 count threshold of 350 cell/mm<sup>3</sup> and/or WHO stage 3 or 4 defining illness (9). A demonstration of reduction in mortality would require large trials with a long follow-up period, given the slower disease progression. Whether or not immediate treatment would provide a clinical benefit had thus not been established. Additional considerations include complexities of providing ART to this age-group – many of these children are orphaned and may not have stable home circumstances, the difficulties faced by healthcare providers in explaining to children how they acquired a highly stigmatised infection associated often with risky sexual behaviour, and that they have a potentially fatal illness, can lead to such discussions being avoided (10).

As ART has become more widely available over the past decade, HIV care services have been increasingly decentralised from secondary to primary health care levels in high HIV prevalence settings, including Zimbabwe, to cope with the very large numbers of people on treatment. Treatment outcomes for adults have been shown to be comparable in both settings. However, there is less data on treatment outcomes for children as many health care settings have been reluctant to treat children in lower level healthcare settings due to the potential clinical and social complexities of treating children.

Zimbabwe has the 5<sup>th</sup> highest HIV prevalence in the world (11). The prevalence of HIV has been plateauing in recent years due to ART roll-out which has seen the mortality from HIV decline as more people gain access to treatment. It is also in

part due to concerted efforts through HIV prevention programmes, to decrease the transmission and acquisition of HIV e.g. strengthening of PMTCT by treating all pregnant women with triple ART on diagnosis of HIV during pregnancy with improved follow up of HIV-exposed infants to ensure early infant diagnosis and early treatment of HIV infection, the roll-out of voluntary male circumcision programmes nationally and a focus on treatment and prevention programmes amongst key populations such as sex-workers and prisoners. Health care and HIV treatment and care are provided nationwide through a government funded four tier health care system- primary care clinics which are located in both rural and urban settings, secondary care clinics or district hospitals, provincial hospitals which are tertiary referral and central hospitals located in the two cities of Harare and Bulawayo, where specialist clinical services are available.

### **1.2 Knowledge Gaps**

- 1) While the course of disease in HIV-infected infants is well understood, less is known about the clinical profile of children diagnosed with HIV infection in older childhood. In particular, older children to date were identified as living with HIV only when they developed AIDS. As provider-initiated testing and counselling has become more established, children are being diagnosed earlier and investigation of their clinical profile is critical for planning appropriate care and management.
- 2) Older children with HIV potentially face complex psychosocial issues which will impact on their ability to manage their illness. A key issue is that many are orphaned and face unstable guardianship which can impact on how they cope with their illness. An understanding of their psychosocial circumstances is thus important to ensure that appropriate services can be developed. The sociodemographic picture of HIV within these children's households has not been teased out.
- 3) Older children (aged > 5 years) are started on ART based on adult criteria. Unlike in younger children, there is no evidence of a benefit in mortality. It is not known whether delaying ART initiation will result in other clinical problems. This is important to understand as earlier start of ART is

associated with potentially negative consequences of toxic effects due to longer ART exposure and the resources required to support adherence in a group with potentially complex social circumstances are lacking.

- 4) At the start of this study, children accessing HIV treatment were largely managed in secondary level health services. With the expansion of paediatric ART programmes, decentralisation of care is required but it is not clear whether outcomes will be compromised as a result (12).

### **1.3 Aim**

The aim of my thesis is to investigate the social and clinical features of HIV infection among newly diagnosed older children and adolescents (aged 6 to 15 years) and to investigate clinical outcomes over an 18 month duration post diagnosis in a decentralised HIV care setting.

My thesis is nested within a larger randomised controlled trial, funded through a Wellcome Trust Intermediate Fellowship grant, no: 095878/Z/11/Z, awarded to Prof Rashida Ferrand, who is co-supervisor of this thesis. The aim of the randomised controlled trial is to assess the effect of community-based support for caregivers of HIV-infected children and adolescents on treatment outcomes (13).

Through planning of this trial, as the MD candidate, I identified key research questions which were feasible to be explored as part of this MD thesis.

### **1.4 Objectives**

- 1) To describe the clinical features of HIV infection in older children and adolescents aged 6-15 year old at time of diagnosis, including clinical and immunological stage, clinical morbidity and ART eligibility.
- 2) To describe socio-demographic characteristics and caregiving arrangements and disclosure status at the time of diagnosis

- 3) To investigate outcomes of HIV treatment among children aged 6-15 years receiving HIV care in a decentralised (primary healthcare) setting.

### **1.5 Outline of thesis**

In Chapter 1, the background to the thesis, the aims and objectives of the thesis and the thesis plan is described.

In Chapter 2, a literature review addressing knowledge gaps in studies surrounding clinical features and outcomes of older children and adolescents accessing decentralised care is described.

Chapter 3 describes the common general methods used in the study including study setting and design, data collection and data analysis.

Chapters 4, 5 and 6 comprise the findings of the study: chapter 4 focuses on the clinical features and chronic morbidity in older children and adolescents at time of diagnosis. Chapter 5, describes the children's socio-demographic characteristics including caregiving arrangements, orphanhood, schooling and disclosure. Chapter 6 refers to the results of 18 month follow up of study cohort including description of incident infections, hospitalisations, deaths and loss to follow up. The main conclusions and recommendations for intervention and future studies are presented in Chapter 7.

## **2. Literature review**

This chapter describes the evolution of the epidemiology of HIV infection in Africa and how it has affected children and adolescents. The recognised clinical and psychosocial challenges are described and knowledge gaps are highlighted to serve as justification for thesis question.

A comprehensive literature review was performed using an online search strategy including PubMed®, Google Scholar and international conference presented abstracts. This was done using the key words of: HIV, adolescents, morbidity, HIV testing, decentralisation and disclosure.

### **2.1 *Human Immunodeficiency Virus***

#### **2.1.1 Origins of HIV**

Acquired Immune deficiency Syndrome (AIDS) was first described in the early 1980's in Los Angeles USA following reports of *Pneumocystis pneumonia* (an opportunistic infection (OI)) in five homosexual men having no apparent immune deficiencies (14). Initially thought to be a syndrome affecting only homosexual men, further cases in heterosexual females in USA, who were partners of men who had signs and symptoms of AIDS, and among recipients of blood transfusion suggested that this syndrome could be found amongst the heterosexual community (15). In 1983, Human T-Cell leukaemia virus (HTLV-3), a retrovirus, was isolated in patients with AIDS and it became apparent that such a virus was responsible for a syndrome which saw previously healthy individuals become susceptible to opportunistic viral, fungal and bacterial infections (16,17). Concurrently, studies from Zaire, Rwanda and Uganda showed a large number of people dying of AIDS, heralding a severe, hitherto unrecognised epidemic, predominantly heterosexually transmitted (18–20).

The role of the subset of T-lymphocyte cells, CD4 cells, in providing an entry point of HTLV-3 into lymphoproliferative system was established in 1984 (21). In 1986, The International Committee on the Taxonomy of Viruses suggested the adoption of the name of Human Immunodeficiency Virus (HIV) for the closely

linked retroviruses being described as causing AIDS but which heretofore had interchangeable names (22). HIV was then subdivided into 2 strains, HIV-1 and HIV-2, the latter being less virulent and found predominantly in West Africa (23,24).

HIV-1 originates from Simian Immunodeficiency Virus (SIV) whose natural host is the chimpanzee subspecies *Pan troglodytes troglodytes* found in Southern Cameroon, Gabon and West Africa and which infected humans through cross species transmission, following from ingesting bush meat which is infected with SIV(25,26). HIV-2 originates from SIV in sooty mangabeys found in Western Africa, but does not exhibit the same virulence as HIV-1 (27).

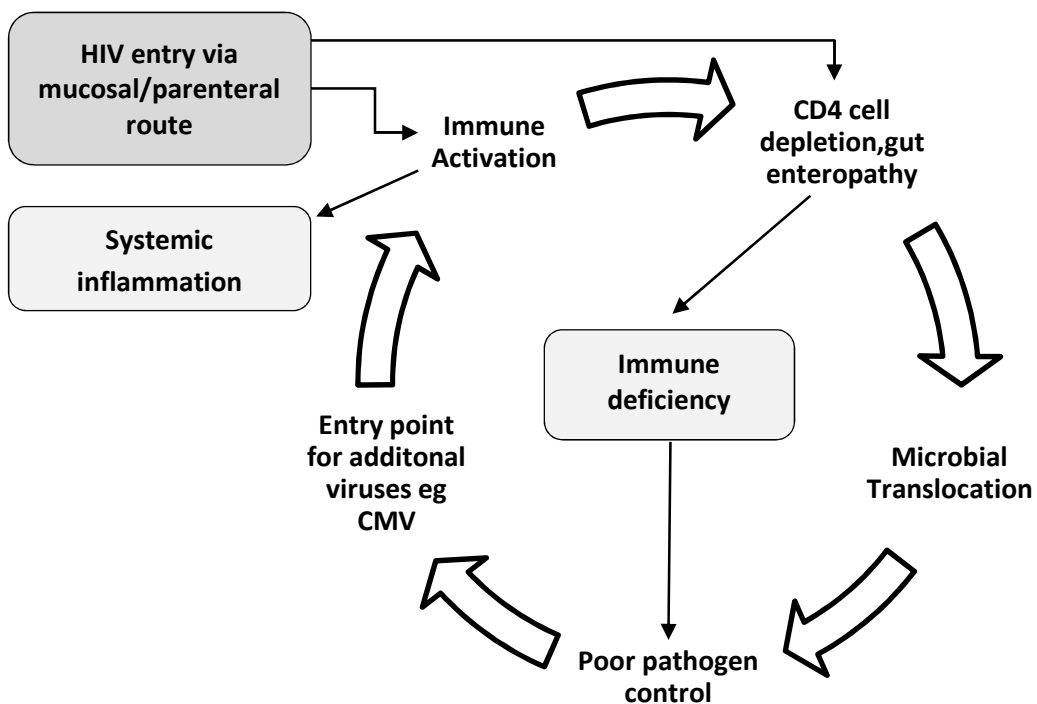
### **2.1.2 How does HIV affect the immune system?**

The inner core of HIV-1 consists of p24 protein which contains 2 copies of single stranded RNA and the necessary enzymes required for initial stages of replication i.e. integrase, protease and reverse transcriptase (28). HIV binds to CD4 T-cell lymphocyte receptors, replicates within the host cell, using reverse transcriptase enzyme to transcribe RNA in to DNA, a second complementary strand of DNA is synthesized so that the double stranded DNA product is integrated into the genome of the host cell with the potential to replicate at any time. The HIV virion then destroys the cell as it emerges, depleting CD4 cells, leading to a progressive depletion and impairment of cellular immunity (29). With the decline in immunity, an individual infected with HIV becomes susceptible to a variety of opportunistic infections (OI) and malignancies and develops AIDS. This occurs over a period of months to years (30). In addition, early during infection, HIV infects gut lymphoid tissue where there is an abundance of CD4 T. This breach of gut mucosal barrier results in a “leaky gut” and allows for microbial translocation across the intestinal epithelium (31). This microbial translocation sets up a pathway for persistent systemic dysregulated immune activation and high levels of circulating pro inflammatory chemokines and cytokines (32,33).

### 2.1.3 Antiretroviral therapy

Anti-retroviral therapy, containing a combination of three different drug classes active at different points of HIV viral replication process, if taken consistently, can control HIV viral replication to limit the destruction of CD4 cells and allow their repletion (34,35). However, HIV-1 has a high mutation rate when it is replicating resulting in many different virus variants called quasi-species. These quasi-species can evade the immune system and also help to foster the development of ART resistance. ART resistance can be acquired through drug selection pressure or transmitted from person to person. The number of mutations necessary to confer resistance to a specific anti-retroviral drug depends on the genetic barrier to resistance of that drug, with some classes of ART having a lower barrier to resistance e.g. non-nucleoside reverse transcriptase inhibitors (NNRTI) which are part of first line treatment regimens in SSA. Intermittent adherence to ART by an individual receiving treatment, particularly with a drug class with a lower barrier to resistance, can allow the virus to replicate and become resistant to one or more of the drug classes used to treat the individual (36).

**Figure 2.1 HIV and Immune activation and inflammation**



Adapted from Douek et al (208)

## **2.2 Epidemiology of HIV in women and children**

In 2015, 36.7 million adults and children were living with HIV worldwide, 53% in sub-Saharan Africa (37). Currently, eastern and southern Africa accounts for 43% of the global total of new HIV infections, however, new HIV infections have declined by 29% from 2010 to 2016 in this region (38). The overall prevalence of HIV has increased in the region due to the widespread roll out of ART which has seen people surviving with HIV infection and conversely there has been a decline in mortality related to HIV infection because of the widespread availability of ART (39).

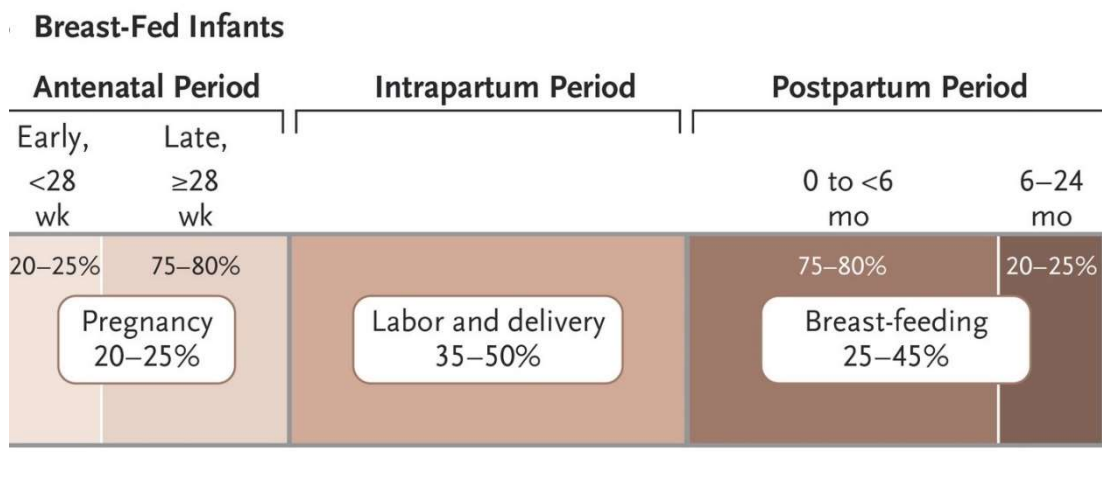
HIV infection in sub Saharan Africa has spread predominantly through heterosexual transmission and much of the region continues to experience a generalised epidemic i.e. the HIV prevalence rate is greater than one per cent in the general population (34,35). Younger women in particular have been disproportionately infected compared to men. There are several reasons for this, encompassing physiological and societal factors. Physiologically, the vaginal tract offers a greater surface area for exposure to infectious seminal fluid and thus serves as an entry point for HIV infection (40,41). Societal and cultural factors in the region mean that women are not empowered to enable them to make behavioural sexual choices compared to men, in a society where men are regarded as decision makers, polygamous relationships are prevalent and it is culturally difficult to negotiate for safer sex (40,42,43).

## **2.3 Mother to child transmission of HIV**

The severe epidemic of HIV among adults in sub-Saharan Africa was followed by high infection rates in children, through vertical (mother-to-child) transmission. Infants exposed in utero to HIV viremia are at high risk of acquiring HIV infection (44–46). Overall the risk of mother-to-child transmission is approximately 25–35% with risk varying over the ante, intra and post-partum periods (see figure 2.2) (47). The French Prospective cohort study of HIV infected pregnant women, in 1993, found risk of HIV infection was highest at delivery (65%) than at other stages of pregnancy, although women surveyed in this study did not breastfeed

their babies and so the risk of transmission through breast milk was not compared (48). Maternal immunodeficiency at time of delivery is associated with a higher risk of transmission (48). Later studies from Brazil in pregnant and breastfeeding HIV infected women also emphasised a weakened immunological status of the mother as a risk factor for transmission alongside having had an amniocentesis in the third trimester as well as breastfeeding, providing a significant opportunity for maternal to child transmission to take place (49). The risk of HIV transmission to breastfed infants is estimated at 16% in those who are fed only on breast milk and should mothers introduce other feeds in addition to breast milk such as water formula feeding, also known as mixed feeding, the risk of transmission is doubled as compared to exclusive formula feeding only (50,51). Caesarean section as a mode of delivery has shown to have a protective effect against HIV transmission to the foetus (52–56). Taking in to account the factors discussed above of high risk of transmission at time of delivery and over the course of breastfeeding, lower immunological status of the mother and the mode of delivery impacting on increased transmission risk, it is not surprising that large numbers of children were being born with HIV infection in late 1990's and early 2000's, following on from the adult peak incidence of infection in Sub Saharan Africa (57).

**Figure 2.2 Relative proportion of HIV infection from untreated mother to infant according to gestational period**



Adapted from Luzuriaga et al (40)

## Chapter 2. Literature review

In 2000, an estimated 600,000 infants were being born annually worldwide with HIV infection (57). At that time, ART was not widely available in low income settings, for adults and expectant mothers, and testing for HIV in pregnant mothers antenatally was not very robust. Many women presented late for ante natal care, and even more would deliver in their own homes with an overall limited access to operative modes of delivery. The practicalities and safety of replacement feeding so as to avoid breastfeeding were difficult for women in low income settings to implement as there was no provision for replacement feeding and cultural challenges meant it was also not acceptable (58). Thus, infants were highly susceptible to acquisition of HIV through maternal routes in an era where methods to control transmission of maternal infection were not widely available. In 1994, Connor et al demonstrated the effectiveness of anti-retroviral therapy in reducing the transmission of HIV infection from mother to infant by almost 66% (44). In this randomised placebo controlled trial, the study showed through a complex, multidose zidovudine regime administered to the expectant mother at ante-and intra- partum stages of pregnancy and to the infant postpartum, that transmission of infection was dramatically decreased. Following on from this, a prospective cohort study in Uganda in 1999, comparing single dose nevirapine (sdNVP) for pregnant woman at time of delivery, followed by nevirapine for the newborn infant, versus zidovudine during intrapartum period for mother and for neonate, showed nevirapine to be more effective in HIV prevention at 16 weeks post-delivery, in breast feeding women (59).

In 2001, acting on the urgent need to find a solution to decrease transmission from mother to child of HIV infection, the WHO adopted a simple ART regime of a single dose of nevirapine to the pregnant mother at time of delivery followed by a single dose of nevirapine for the new-born infant, given within 72 hours of delivery if the expectant mother did not meet the CD4 count criteria of  $<350\text{cell}/\text{mm}^3$  to commence triple ART (60). Such a regimen was thought to be a simple and more feasible approach to reduce mother to child transmission in high HIV burden settings. However, this regimen still required access to antenatal care and uptake of HIV testing for pregnant women to be able to access single dose nevirapine. To simplify and improve uptake of ART among pregnant women

## Chapter 2. Literature review

and strengthen PMTCT programmes, “opt out” HIV testing, whereby patients must explicitly refuse a HIV test, promoting a simplified approach to pre-test HIV counselling in antenatal services. This was introduced by WHO in 2007 (61–63).

Over the past decade there has been an evolution of PMTCT regimens in low-income settings, moving away from sdNVP, to the use of triple ART (64). This is due to the fact that combination ART dramatically reduces transmission risk from mother to child, and its recommendation was termed Option B, following on from Option A, it defined by use of triple ART for pregnant mothers from time of diagnosis until period of breast feeding had ended. This PMTCT recommendation was then further modified and named Option B+ where pregnant mothers remain on lifelong ART even after ceasing breastfeeding which protects their health and ensures future pregnancies are catered for in preventing MTCT (see table 2.1) (65). It was also brought about due to concerns about the potential of infants to acquire resistance to nevirapine treatment, which formed part of the first line ART regimen in treating children living with HIV. If a child subsequent to having received nevirapine prophylaxis post birth tested HIV positive his exposure to nevirapine, albeit for a short period of time, may mean that his now triple ART regimen may not be effective due to archived resistance to nevirapine and its drug class NNRTI.

Current WHO recommendations are to test expectant women at each point of contact with health care personnel- at the pregnancy booking visit, at time of delivery of infant, at 6 weeks post-partum and also at the completion of breast feeding period to ensure a timely HIV diagnosis (66). With the evolution of guidelines there has been a 70% decline amongst new HIV infections in children, worldwide, from 2000-2015 (67).

Until such time as such services could be streamlined, there was a delay in diagnosis of HIV antenatally and postnatally and HIV-exposed children and subsequently HIV infected children were not being identified through testing in a timely manner, so called early infant diagnosis (EID). Testing of HIV-exposed infants through HIV-DNA polymerase chain reaction (PCR) testing at 6 weeks

after birth is the recommended standard of care to determine HIV infection in early infancy. If found to be negative the child should then be retested at the end of the breast feeding period to determine if MTCT may have occurred through breastfeeding. If found to be infected then ART initiation occurs immediately. However, there are recognised gaps in this testing cascade including, registration of HIV-exposed infants to ensure testing at 6 weeks is performed, timely turnaround of PCR results which are performed at central laboratories and also whether the results are conveyed to the caregiver to ensure linkage to HIV services, if found to be infected (68).

**Table 2.1 WHO PMTCT Options**

	Woman receives		Infant Receives
	Treatment (CD4 <350 cells/mm <sup>3</sup> )	Prophylaxis (CD4>350 cells/mm <sup>3</sup> )	
<b>Option A<sup>a</sup></b>	Triple ARVs for life	Antepartum: AZT Intrapartum: sdNVP + AZT/3TC Postpartum: AZT/3TC x 7days	NVP continued x 1 week post breastfeeding Or NVP 4-6 weeks if no breast feeding or mother on triple ART
<b>Option B<sup>a</sup></b>	Triple ARVs for life	Triple ARVs discontinued post breastfeeding	NVP 4-6 weeks regardless of infant feeding method
<b>Option B+<sup>b</sup></b>	Triple ARVs for life		NVP 4-6 weeks regardless of infant feeding method

<sup>a</sup> WHO 2010 guidelines <sup>b</sup> WHO 2013 guidelines

## **2.4 Natural History of HIV infection**

Unlike in adults, where time to progression of AIDS from time of acquisition of HIV infection is close to 10 years, without ART, the natural history of HIV infection in infants is quite different (68). It is characterised by fast disease progression, with over one third infants dying in the first year of life without antiretroviral treatment in Africa (4). Common clinical features include failure

## Chapter 2. Literature review

to thrive and oral candidiasis and OIs such as pneumocystis pneumonia, cytomegalovirus and herpes simplex and diarrhoeal illnesses (69–71). Progressive encephalopathy is also described leading to failure to attain significant development milestones or loss of developmental milestones, impaired brain growth or acquired microcephaly and/or acquired symmetric motor deficit (72).

Given the high mortality rates reported in infancy, it was assumed that survival beyond early childhood in the pre-ART era was exceptional. However, as HIV epidemics matured, there were reports of increasing numbers of older children and adolescents presenting to health services in sub-Saharan Africa with features suggestive of longstanding HIV infection and mother-to-child transmission as the most likely mode of acquisition. Features consistent with MTCT included high rates of maternal orphanhood, natural sibling deaths and no report of sexual debut or blood transfusion, with a low prevalence of HSV-2 infection amongst adolescents presenting with HIV infection, which can be perceived as a marker of horizontally acquired HIV infection (5,73).

It is now estimated that at least a third of African HIV-infected infants have slow-progressing disease with a median survival of at least 16 years without treatment, with no upward estimates available due to the lack of empiric data. Two modelling studies have predicted similar survival rates of long term non progressors, one study estimating survival of 13% of long term non progressors to 10 years of age, the second study estimating a 17% survival to 17 years of age (74,75). Ferrand et al have predicted an peak in emergence of mother to child transmission survivors across high epidemic settings in this current decade (76).

Notably, cohorts in high-income countries had demonstrated presence of perinatally infected “long term non-progressors” of HIV infection. The largest, a French cohort, which followed 348 participants and defined non-progression as HIV-1 infected children observed for at least 10 years who remained ART naïve, who remained clinically asymptomatic and retained immunological control, found that 2.4% had not had disease progression by 10 years of age (77).

However, these were relatively small numbers and the availability of ART in the late 1990s changed the course of disease among children.

Unlike infants, where the large numbers born and dying with HIV were immediately obvious, the substantial burden of vertically-acquired HIV among older children and adolescents in Africa was recognised much later due to i) the time required to grow up and present with HIV-related disease in later childhood ii) prior assumption that survival to older childhood was not possible and therefore no cohorts of children were followed up beyond early childhood and iii) lack of the typical HIV-related infections developing until adolescence. It has been suggested that the large numbers of slow progressors in Africa may partly be explained by the continued practice of breastfeeding as several studies have shown HIV infection post-partum through breastfeeding is associated with slower progression than infection acquired during the intra-uterine period (78–80).

### ***2.5 Clinical features of HIV in “slow-progressors”***

Contrary to the more typical picture of AIDS observed in children with fast-progressing disease, slow-progressors have a more indolent course of infection. Minor illnesses such as upper respiratory tract infection, including recurrent otitis media and fungal skin infections, which are also not uncommon in HIV uninfected children, do not prompt HIV testing, although provider initiated testing and counselling (PITC) is standard of care in high HIV burden settings. This has led to children growing up with undiagnosed HIV infection and presenting much later, often times to tertiary care settings with much more advanced HIV illness (6,81).

Similarly, growth delay i.e. stunting of growth (decreased height for age z scores) and wasting (decreased weight for age z scores) have been documented amongst children at time of ART initiation (82,83). While a recognised consequence of living with HIV untreated, in low-income settings, growth failure may also be a

consequence of nutritional and social deprivation and therefore may not trigger a healthcare provider to offer HIV testing.

Delayed pubertal development is a recognised complication of adolescents living with perinatally acquired HIV infection. De Martino et al compared age of puberty onset in 212 adolescents based on point of entry into Tanner stage P2 or B2 for girls and P2 or G2 for boys (84). The HIV uninfected comparison group of 843 girls and 821 boys provided the reference range. The HIV infected group had noted pubertal delay in both gender groups, females having a having a greater period of delay than males. Age at puberty was unrelated to clinical or immunological correlates. This study was in an Italian cohort of children which may not necessarily be generalisable to African ethnicity pubertal development but was an early study indicating effects of HIV infection on adolescent development. A larger U.S. cohort of over 900 boys and girls aged between 6 and 18 years had Tanner stage assessed at 2 or more intervals and were compared to U.S. Tanner stage reference range NHANES 3 (85). Immunosuppression at time of Tanner staging was associated with delayed pubertal development in both girls and boys.

Features of chronic morbidity amongst older children living with HIV have begun to be more recently described including effects on respiratory, cardiac and neurological system (86,87). Older children report symptoms of chronic cough and display reduced exercise tolerance (87). Subtle chest X-ray anomalies have been described in cross sectional studies and high resolution computed tomography scanning demonstrates a pattern of decreased attenuation suggesting small airways effects, contrasting to features of lymphoid interstitial pneumonitis more commonly seen in younger children living with HIV infection (88).

There is a lack of data on description of clinical features of older children and adolescents who present with established HIV infection but have not received ART. Such descriptions would serve to inform on the natural progression of HIV in children with slow progressing disease.

## **2.6 ART among children**

ART availability has substantially reduced the mortality and morbidity witnessed in pre-ART era and has changed the course of the HIV epidemic in both adults and children (89). Successive revisions of ART guidelines, following evidence of decreased morbidity and mortality if HIV treatment commences at higher CD4 levels rather than deferring ART start until CD4 declines, has seen WHO moving to adopt the approach of treating both adults and children with ART at time of HIV diagnosis, regardless of their CD4 counts (90).

While the evidence is strong for this in adults, the survival benefits for starting ART at time of diagnosis in infants has also been robust. The landmark CHER trial showed that starting ART in infants, at time of diagnosis rather than waiting for a decline in CD4 measurement or presence of advanced HIV infection saw a 76% relative reduction in mortality in those who started ART on diagnosis (8). This led to a change in WHO guidelines in 2010 which saw all children under two years of age starting ART at time of diagnosis (91).

There is clear evidence that immediate ART in infants impacts mortality. Evidence for when to start ART in older children is lacking. Schomaker et al performed a modelling study to determine the difference in mortality between immediate ART start or delaying ART until CD4 levels decreased as per guidelines at that time, in children 2-5 years attending for care in Southern Africa (92). The study noted that there was no mortality difference up to three years after ART start between the two groups although the lower the CD4 count at ART initiation the higher point estimates there was for mortality. Puthanakit et al found no mortality difference in a randomised controlled trial comparing outcomes in early versus deferred ART for children aged 1-12 years although it was an under powered trial (93). Despite the lack of evidence of when to initiate ART in children, in 2013, as per WHO guidelines all children under 5 years of age started ART at time of diagnosis (9).

The dilemma of timing of ART start in children is a complex issue due to the recognised complexities of administering ART to children. Medication formulation, more complex pharmacokinetics and pharmacodynamics in children have to be considered when commencing drugs with the aim of achieving maximal virological suppression (94,95). Added to this is the often perceived complexities of weight based ART dosing, which requires children's doses to be adjusted according to weight increase or decrease. There have been previous reports of children being under dosed according to weight requirement which may set up a potential for future drug resistance (96).

There is a recognised delicate balance between need to take ART once decline in CD4 occurs, but in advance of decline in WHO stage disease, versus the difficulties in adhering to treatment and the potential toxic side effects due to the fact of a requirement of longer life time exposure to ART than an adult will need (97). Challenges in ART roll out for children have been augmented because of the perceived additional complexities in caring for children living with HIV, as described below.

### ***2.7 Psychosocial impacts of HIV infection***

The HIV/AIDS pandemic has left more than 12 million children orphaned globally as of 2015. As expected, there is a strong association between orphanhood and HIV status, both due to orphans being at higher risk of having acquired HIV through their parents but also being more vulnerable to acquiring HIV infection (98). Orphaned children grow up in households where the traditional family structure is fragmented and have to cope with the loss of one or both parents which can have far reaching psychosocial effects, including poverty, lack of parental guidance, dealing with bereavement. Schooling can be affected by orphanhood due to a lack of school fees within a household where children who are extended family members are not seen as a priority (99).

Older children report feeling stigmatised and discriminated by their illness both in their own households and in the wider community (99). Caregivers report that

they worry about the stigmatising effect attendance at a clinic, for HIV treatment, might have on the child in their care (100).

A major event for a child living with HIV is that of disclosure (becoming aware) of their HIV status. Disclosure rates for children and young adolescents remain low, ranging from 2% to 57% according to caregivers interviewed in sub Saharan African settings (101).

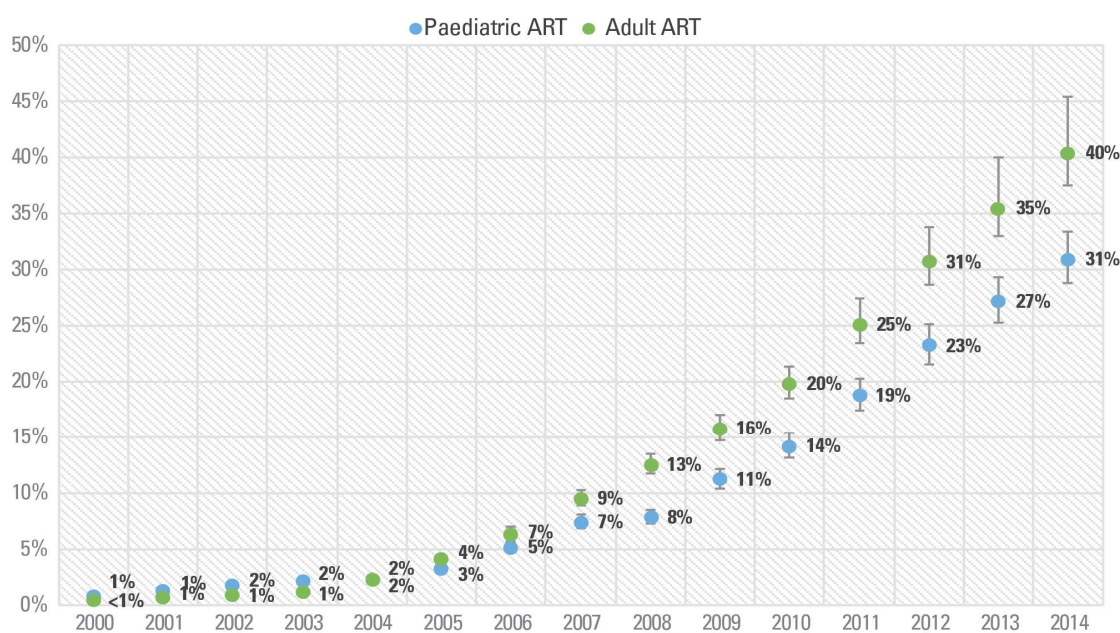
**Table 2.2 Complexities of ART for children and adolescents**

<b>Physiology of Children</b>	<ul style="list-style-type: none"> <li>– Weight based dosing requirements</li> <li>– Malabsorption</li> <li>– Exposure related ART toxicity</li> </ul>
<b>Psycho-Social Challenges</b>	<ul style="list-style-type: none"> <li>– Disclosure</li> <li>– Adherence</li> <li>– Orphanhood</li> </ul>
<b>Access to Care</b>	<ul style="list-style-type: none"> <li>– Distance to travel to secondary care facilities</li> <li>– Lack of health services knowledge of clinical needs for youth</li> <li>– Nurse-led care challenges</li> </ul>

In summary, children growing up with HIV face multiple challenges apart from the physical complications of HIV infection. Death within the family, orphanhood, and discussion of their HIV status is often times limited which can affect their future adherence to ART and thereby their well-being. The decentralisation of care to primary care clinics may help to increase younger person’s access to ART, however whether outcomes once initiated on ART can be more favourable than secondary level facilities in an era that now treats all children on a diagnosis of HIV infection remains to be seen.

## **2.8 Access to HIV care and treatment for children**

There remains a substantial gap in access to ART for children under 15 years compared to adults, worldwide (Figure 2.3). This gap in access to ART may well be due to the psychosocial factors described above making it more difficult for children within a household to attend for HIV care and treatment and this gap in accessing treatment may also explain why adolescent’s HIV mortality rates are rising compared to all other age groups.

**Figure 2.3 Proportion of children and adults accessing ART over time**

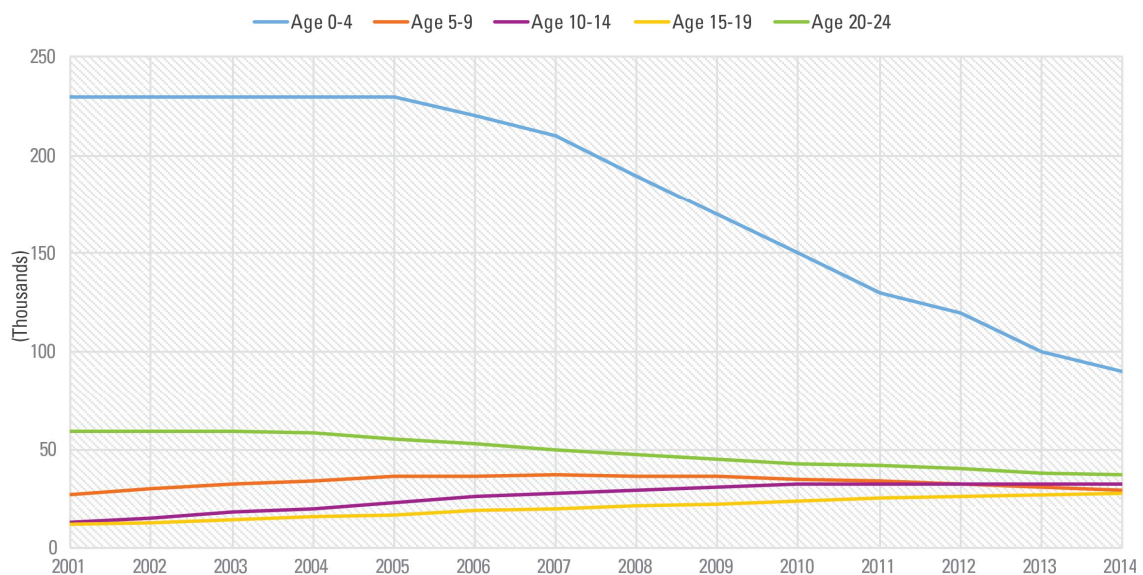
**Source:** UNAIDS/UNICEF/WHO Global AIDS Response Progress Reporting and UNAIDS 2014 HIV and AIDS estimates, July 2015

Johnson et al, in a modelling study predicting mortality effect of increased availability of testing and treating of infants has predicted better outcomes for infants, however, the study predicts ageing of the paediatric HIV epidemic and a shift towards older children requiring treatment and availing of HIV care programmes (102). In 2015, HIV related mortality had decreased from 2005 across all age groups, except for adolescents (defined as 10-19 years of age) for whom mortality had actually increased by 50% (figure 2.4)(103).

The recognition of the need to increase access to care for all age groups has been made for some time now. In 2006, WHO recognised that the traditional model of physician led HIV care (as seen in high-income settings) was not feasible in resource limited settings to enable the ever growing numbers of people living with HIV to access treatment and care. A chronic shortage of doctors and higher level health personnel meant that secondary and tertiary level centres were not able to meet the demands of ever growing numbers requiring HIV treatment. PLHIV themselves were not able to access care due to distance to travel to receive such interventions. Because of these factors, WHO advocated for a public health approach, with decentralization of care, task shifting from doctors to nurses of

ART initiation and greater community support in form of treatment support groups (104). Early comparison studies between hospital based and primary care clinics performed in rural settings in South Africa and Lesotho demonstrated encouraging outcomes at one year and two year follow up respectively (105,106). Although the focus was on ART provision to adults in both programs and therefore potentially not indicative of paediatric decentralised care, LTFU rates were lower in primary care clinics compared to hospital based care at one year in South African setting (19% vs. 2%,  $p < 0.001$ ) and Lesotho programme demonstrated a 77% alive and retention in care rate at 2 year follow up of over 13,000 adults and children enrolled in primary health care clinics.

**Figure 2.4 AIDS related deaths among children, adolescents and young adults**



**Source:** UNAIDS, 2014 HIV and AIDS estimates, July 2015.

Similar success in decentralization of paediatric care was reported in an Ethiopian retrospective review over a 5 year period up to 2012, showing almost equal rates of ART initiation between primary and secondary level facilities although worryingly the overall rate of LTFU was 34% (107). Notably, secondary care level facilities had a higher proportion of infants enrolled and deaths recorded, as well as participants at this site having overall lower median CD4 counts. The trend of children receiving care being younger and potentially sicker

at secondary care facilities is not in itself an issue but rather may well point to the role which such secondary and tertiary level care facilities should provide, allowing transfer out of well, stable patients to primary care facilities enabling secondary level facilities focus on those requiring physician and clinical investigational backup.

### **2.9 Summary**

The predicted increase in older children and adolescents accessing HIV care services through the aging of the infant cohort of children living with HIV but also through improved HIV testing strategies to identify older children living with HIV, who have escaped infant testing initiatives, may find healthcare services and programmers under-prepared in treating children and adolescents.

The clinical features of older children and adolescents accessing such services have not been well articulated and therefore it will prove difficult for health service providers to plan for adolescents care if these are not elicited. The psycho-social needs of children living with HIV are many and complex and further teasing out of children's social backgrounds and how supports within their family may or may not aid children in engaging in care deserves further teasing out.

As decentralised care has been available for adults for some years but has been slow to roll out for children, it is important to understand how youth may fare in such a system and whether nurse-led care would be able to manage and treat their potential co-morbidities warrants further description.

The ambitious 90-90-90 target as set by UNAIDS means that 90% of people living with HIV will know their status, 90% should be able to access treatment and 90% should be able to achieve virological suppression sets a tall order for health care providers (1). The ever changing world of treating people living with HIV has seen younger children receiving much attention, understandably so given their high mortality rate without treatment. In an era of decentralisation and task shifting approach to HIV management as well as concerted efforts to engage

## Chapter 2. Literature review

children and youth in HIV programmes, the need to understand their physical conditions and social challenges is necessary to ensure preparedness on behalf of service providers but also to improve children's futures.

### **3 Methods**

This was a prospective cohort study performed from January 2013-June 2016. Evaluation of clinical and sociodemographic features was made at the baseline visit.

Methods which are common to all three results chapters are described here. Methods in relation to individual studies are detailed within each chapter.

#### **3.1 Setting**

Zimbabwe has a population of just over 13 million (ref Zimstat). The prevalence of HIV infection among adults peaked at 29% in 1997 based on antenatal care surveillance at the time (108). The prevalence of HIV has steadily declined since then and according to a national household based national survey in 2015, the prevalence of HIV amongst adults aged 15-64 years is 14.6% (95% CI 14-15.3)(109). The national PMTCT programme had been strengthened increasing its coverage from 22% in 2007 to 93% in 2013 (110). At the time of this study commencement in 2013, Zimbabwe's ART coverage for children less than 15 years was only 30% compared to 60% for adults (111).

In 2007, the WHO recommended provider initiated HIV testing and counselling (PITC) for countries experiencing generalised HIV epidemics (112). Zimbabwe adopted this approach at the time and it remains standard of care throughout all health care facilities where HIV testing is free of charge. HIV care for adults has been decentralised to primary care level facilities, however, care and management of children and adolescents remained at secondary level facilities nationally in 2013.

The study was conducted in seven primary care clinics in Harare. Primary health care clinics are under the management of municipal health services (Harare City Health Directorate) and provide primary care services throughout the city. The clinics were situated within seven communities in south west Harare, namely Dzivaraeskwa, Mufakose, Budiro, Kwadzana, Glenview, Highfield and

### Chapter 3. Methods

Rutsanana. The communities chosen were purposively selected on the basis that they had a high population of children under 15 years and the clinics were already initiating ART and providing follow-up HIV care for HIV-infected adults, and therefore it would be feasible to introduce this for children as well. It would also ensure ease of hand-over of care of study participants to clinic staff on completion of the study. All primary care clinics under the auspices of City of Harare management follow Zimbabwe national guidelines for care and management of HIV, therefore, alleviating a potential bias in selection of clinics.

The US\$ has been the official currency in Zimbabwe since 2009. The gross domestic product in Zimbabwe was \$1026.4 per capita in 2013, the time of study initiation (113). US\$1 would buy one loaf of bread, US\$ 3.40 would buy two litres of cooking oil. Primary care facilities in Harare offer nurse-led acute and chronic care incurring a cost of US\$5 per visit. A HIV consultation is offered at a reduced cost of US\$1 per visit. ART and cotrimoxazole are provided free of charge. A designated physician visits on a weekly basis complementing case management provided by nurses and reviewing patients referred by nursing cadre, who may have more complex conditions.

The research team consisted of three research nurses who were based between the seven selected primary care clinics. Based at the research head office, 20km away from the research sites, was the research management team. This consisted of the Principal Investigator of the Zenith Study and MD supervisor, Prof Ferrand, data manager and two data assistants who were responsible for data entry and ensuring security of the data entered. Support staff in the form of the trial coordinator, administration assistant and project finance officer were also located at the office.

Visiting colleagues from London School of Hygiene and Tropical Medicine consisted of trial statisticians Professor Helen Weiss and Victoria Simms. Advice was sought from Victoria Simms on design of analysis of outcomes in chapter six.

### **3.2 Enrolment**

The period of enrolment was from January 2013-December 2014. Follow up was for 18 months from date of enrolment.

All children aged 6-15 years who attended any of the 7 primary care clinics during this period from Monday to Friday each week and who tested HIV-positive through PITC at the study clinics were offered enrolment into the study. Age and date of birth were confirmed through birth registration certificates. In the case of birth registration certificates not being available, parental or guardian verbal confirmation of date of birth was used to ascertain age. Research assistants supported HIV testing at each clinic site and referred any child found to be HIV-positive to the research nurse on site. The research nurses then assessed eligibility based on the criteria described below.

#### **3.2.1 Inclusion criteria:**

1. Age 6-15 years
2. Resident in Harare and planning to access HIV care at one of the study PHCs
3. Guardian consent and participant assent
4. Newly diagnosed with HIV or previously tested HIV positive but had not registered with care.

#### **3.2.2 Exclusion criteria**

1. Residing outside of clinic catchment area
2. No guardian consent or child assent obtained
3. Guardian chose to access care for child at a different clinic

Those who did not consent to participate could still receive care at the PHC but their data would not be used for the study. Those who sought to seek care elsewhere were provided with a referral for onward care.

### **3.3 Ethical Considerations**

Ethical approval for the study was obtained from Medical Research Council of Zimbabwe, the ethics committee of Harare City Health Department, Biomedical

Research and Training Institute Institutional Review Board and the London School of Hygiene and Tropical Medicine ethics committee. Written informed consent was obtained from all caregivers in their choice of either Shona or English language. Children aged 6-12 years were given a simpler consent form with age-appropriate information. If children were unable to write, verbal assent was obtained as well as a thumb print on the consent form. Children 13 years and above were asked to sign a consent form with more detailed information regarding study participation than was provided to those 12 years and under. Disclosure of HIV status by guardian or member of the research team to the child was not a prerequisite for enrolment. A record of child's knowledge of HIV status was kept by research nurse to ensure non-accidental disclosure at a subsequent study review.

### ***3.4 Laboratory Methods***

#### **3.4.1 HIV Testing and CD4 counts**

HIV testing was performed by a trained counsellor using rapid diagnostic test kits. Alere Determine™ was initial test and confirmatory rapid test was SD Bioline. First Response® 1-2-0 Card test was introduced as the confirmatory test in April 2013. The tie breaker rapid diagnostic test (in the event of test 1 and 2 being discordant) was Chembio HIV 1/2 Stat-Pak® assay. CD4 count was measured using Alere PIMA™CD4 machine. 3mls of blood were drawn by research nurse and collected in an EDTA tube. Samples were transported daily to a central laboratory for processing.

### ***3.5 Data management***

Data was collected on paper case report forms, pre-designed by trial team. Research nurses administered the questionnaires to participants and their caregivers at each visit. Each form was logged on a daily basis at the study site and delivered by the study driver to the data office daily. Medical records of each child were kept at the study site in a locked cabinet. Data forms were then scanned by optical mark recognition (Cardiff TELEFORM Intelligent Character, Version 10.7) by a data clerk at the research office. Data entry was performed by

### Chapter 3. Methods

the data clerk on scanning of each form, whereby interactive verification and correction of data using the Teleform optical recognition system was carried out and optional plausibility visual checks were also performed. Such a method meant that double-entry of data was not required. Data was then stored in a central database server, which was password protected and only accessible by the data manager and data assistants.

Upon entry of data, data cleaning by MD candidate was performed on a monthly basis through assessing for missing data, ensuring numerical variables were within acceptable ranges for changes over time e.g. height and weight and cross checking of electronic stored data with paper forms through manual checks. Analysis of data was performed using STATA, version 12.1 (STATA Corporation, USA).

## **4. Clinical profile at HIV diagnosis**

### **4.1 Introduction**

Untreated, vertically-acquired HIV infection is associated with high mortality rates. Observations amongst African infant cohorts in the pre-antiretroviral therapy era, noted there was an estimated 50% probability of dying from advanced stage HIV infection by two years of age (4). However, as HIV epidemics matured substantial numbers of perinatally-infected children were reported to be presenting with HIV infection for the first time in later childhood or adolescence (75,79,114). Survival estimates have subsequently been successively revised upwards and it is estimated that a third of HIV-infected infants experience slow-progressing disease with a median survival estimated to be at least 16 years (76).

Unlike children who have rapid disease progression and present with AIDS-defining illness in infancy, children with slow progressing HIV are either paucisymptomatic or typically have a history of multiple, non-specific complaints, including recurrent upper respiratory-tract or skin infections that are also common among their HIV-uninfected peers (5,115). Recognition of HIV is consequently often delayed until presentation with advanced disease (5).

There is strong evidence that immediate initiation of ART reduces mortality in infants, in particular those under 1 year of age (4). The WHO 2013 HIV treatment guidelines recommend immediate ART initiation on diagnosis regardless of clinical or immune stage in all children aged under five years (9). Such a benefit has not been demonstrated for older children (116). For those over five years, WHO 2013 guidelines (which were standard of care when this study was being conducted) recommended that, as for adults, ART is deferred until the clinical Stage 3 or 4 HIV disease is apparent or if the CD4 count drops below 500 cell/mm<sup>3</sup> (9). In 2015 the WHO further revised HIV treatment guidelines recommending that ART be commenced in all age groups regardless of clinical or immune status, although evidence for immediate ART commencement is lacking in older children and adolescents (117).

While the risk of AIDS-defining infections is low above a CD4 threshold of 500 cells/mm<sup>3</sup>, longstanding infection is associated with development of chronic complications, which may not fulfil the criteria for ART initiation (118). For example, already documented is a high prevalence of chronic respiratory symptoms among adolescents with vertically-acquired HIV infection. However, objective measures of lung function were not performed and the study included both ART-naïve and ART-treated individuals (87).

We investigated the prevalence of chronic symptoms, including a standardised assessment of growth and lung function and whether these were associated with immunological status among children aged 6-15 years at HIV diagnosis of HIV infection.

### **4.2 Methods**

#### **4.2.1 Study setting**

A cross sectional study was carried out in seven public sector primary healthcare clinics. Prior to the commencement of this study, HIV care had been initiated at secondary level institutions throughout Zimbabwe and children and adolescents were only referred to “step down” primary health clinics for ongoing care once “stable” on ART. Children attending for routine medical care at primary care clinics receive nurse-led care and are managed using WHO Integrated Management of Childhood Illness (IMCI) protocols with referral to the local hospital where required (119).

#### **4.2.2 Clinical Assessment after diagnosis**

The clinical history was recorded using a nurse administered questionnaire. Previous contact with health services, history of past illness, previous exposure to ART including maternal ART for prevention of mother-to-child HIV transmission (PMTCT), drug history, and acute and chronic symptoms were recorded, including respiratory and gastrointestinal symptoms, and problems with hearing, vision, speech and gross motor function. HIV infection was staged using the WHO Staging System and a CD4 count was performed (120). TB

screening was performed through WHO TB screen questionnaire and if participant answered positively on any question, sputum was obtained for testing for mycobacterial tuberculosis using GeneXpert (121).

### **4.2.3 ART eligibility and regimens**

HIV treatment followed national guidelines (Appendix A). Until February 2014, participants were initiated on ART if their CD4 was below 350 cells/mm<sup>3</sup> or had WHO Stage 3 or 4 infection (122). From March 2014, Zimbabwe adopted the WHO 2013 consolidated guidelines, with the threshold for ART initiation revised to 500 cells/mm (9). All children were commenced on cotrimoxazole prophylaxis at diagnosis of HIV infection.

As part of the study, nurse-led assessment for ART eligibility, initiation of ART and ongoing care was introduced at the study clinics (decentralised HIV care) for children, with supervision from a study physician. Nurses were trained on HIV counselling and management including WHO staging, ART side effects and weight based ART dosing according to the national guidelines. The study physician was consulted over the phone if there were any queries and reviewed participants at the nurse's discretion.

According to Zimbabwe National guidelines- children >6 years and ≤12 years were prescribed zidovudine/lamivudine and nevirapine, dose adjusted for weight. For a child aged >12 years and/or >35kg, tenofovir/lamivudine and nevirapine was recommended as first line treatment. Efavirenz was recommended if a child developed a suspected drug reaction to nevirapine or required concomitant treatment for TB. In March 2014 the national guideline was changed so that tenofovir/lamivudine and efavirenz for those >12 years and >35kg was recommended as first line treatment (81).

### **4.2.4 Physical Examination**

A standardised physical examination was carried out, including inspection of the skin for herpes zoster scarring, papular pruritic eruptions, plantar warts, verrucous warts, molluscum contagiosum, fungal infection and Kaposi sarcoma.

The oral cavity was examined for gingivitis, periodontitis, candidiasis and Kaposi sarcoma. Anthropometric examination included measurement of height and weight. The head circumference was determined by measuring the greatest occipito-frontal circumference, with the larger of two readings recorded. Tanner pubertal staging was performed in children aged 10 years and above (Appendix B)(123). In females, breast and pubic hair development and age at menarche were recorded. In males, testicular volume measured using a Prader orchidometer, pubic hair development and penile length were assessed.

### **4.2.5 Respiratory Assessment**

Cardiorespiratory function was assessed by the Medical Research Council Dyspnoea Scale and modified incremental shuttle walk test (ISWT) with pre- and post- test recording of respiratory rate, heart rate and peripheral oxygen saturation using a pulse oximeter (124,125). ISWT was not performed if baseline oxygen saturation was less than 88%, or if resting heart rate or respiratory rate exceeded 120 and 30 per minute respectively. Spirometry was performed by trained nurses using an EasyOne™ World spirometer (NDD Medical Technologies, Inc., Andover, MA, USA). After demonstration of the procedure, the participant performed forced exhalation manoeuvres while seated until quality criteria had been reached or 8 trials had been completed. The trial with the highest forced expiratory volume at one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were selected for interpretation. Reversibility testing was carried out if either obstruction (FEV<sub>1</sub> less than lower limit of normal and a reduced FEV<sub>1</sub>/FVC ratio) or restriction (FVC less than lower limit of normal and a normal or increased FEV<sub>1</sub>/FVC) was found on the best selected trace. This was done by administering 200mcg inhaled salbutamol via spacer and repeating spirometric testing 15 minutes post salbutamol administration (126).

### **4.2.6 Clinical definitions**

A z-score of <-2 for height-for-age and weight-for-age were considered to represent stunting and wasting respectively. Pubertal delay was defined as girls not having reached Tanner 2 breast development by age 12 years and boys not having reached Tanner 2 testicular volume by age 14 years (127). An obstructive

lung defect was defined as FEV1 less than 1.64 standard deviations (SD) below the mean and FEV1: FVC of less than 1.64SD below the mean. A reduced FVC (which would be suggestive of restrictive defect) was defined as an FVC below 1.64SD below the mean with a normal or increased FEV1: FVC ratio (128). Reversibility of either obstructive or restrictive defect was defined as greater than or equal to 12% improvement in FEV1 after repeat spirometric testing post administration of salbutamol (126).

#### **4.2.7 Data analysis**

Z-scores for height-for-age, weight-for-age and head circumference-for-age were calculated using the 1990 British growth reference curves (129). WHO references are available for children for height- and weight for-age but those for weight-for-age are only available for children up to age 10 years and therefore British growth references were used. Spirometric indices were expressed as z-scores using GLI2012 reference ranges (128). The association between the a priori defined variables defined as: WHO stage 3 and 4, self-rated general health fair/poor in the past 3 months, documented chronic skin condition, height for age z-score <-2, weight for age z score <-2, head circumference for age z score <-2, pubertal delay, visual impairment and hearing impairment and the outcomes of CD4 count <350 cells/mm<sup>3</sup> and CD4 count <500 cells/mm<sup>3</sup> was determined using logistic regression on univariate analysis adjusted for age and sex. Missing variables were excluded in logistic regression analysis.

### **4.3 Results**

During the study period 9,655 children were tested for HIV, of whom 449 (4.6%) tested HIV-positive. An additional 21 participants were identified who had been diagnosed prior to study commencement but had not engaged in care and/or had not commenced ART. The median duration between HIV diagnosis elsewhere and engagement with care through our study, was 3.2 years (interquartile range (IQR) 0.14-13.0). In total, 385 (86%) participants were recruited into the study. The remainder were not enrolled due to residence outside the study area (n=24, 5%), declined consent (n=25, 5.5%), care sought at a clinic outside of study area

(n=34, 7.5%) and were outside of age recruitment window on confirmation of date of birth (n=2, 0.4%).

### **4.3.1 Clinical Characteristics and demographics**

The median age at diagnosis was 11 years (IQR 8-13) and 52% were female. The majority of participants were infected through mother-to-child transmission (n=366 (95%)) based on a history of maternal or natural sibling HIV or death, and self-report of no sexual debut, blood transfusions or surgery. Less than 2% of mothers of participants had received ART for PMTCT. Although 78% of participants had attended a PHC in the past 6 months and/or been previously hospitalised, HIV testing had not been performed. Additional opportunities for HIV testing that were missed included previous TB treatment n=18 (5%), recurrent upper respiratory tract infection n=107 (28%) and previous herpes zoster infection n=41 (11%) (Table 4.1).

### **4.3.2 Stage of HIV infection**

The median CD4 count at diagnosis was 375 cells/mm<sup>3</sup> (IQR 215-599). Sixty five percent of participants had a CD4 count of less than 500 cells/mm<sup>3</sup>. Despite the relatively low median CD4 count at presentation, 229 (59%) participants had WHO stage 1 or 2 disease.

### **4.3.3 ART eligibility**

Using a CD4 count threshold of  $\leq 350$  cells/mm<sup>3</sup> and/or WHO stage 3/4 disease, which was the Zimbabwe national guidelines at the time of this study commencement, 67% children were eligible for ART. In 2014, Zimbabwe national guidelines for ART eligibility were changed reflecting WHO recommendations. This saw the CD4 count threshold for ART initiation change to  $\leq 500$  cells/mm<sup>3</sup> and/or WHO stage 3/4 disease being present. Such a threshold cut-off meant that 78% of participants were eligible to commence ART once these guidelines were implemented nationally.

#### 4.3.4 Chronic clinical conditions

More than half of participant's caregivers (n=197 (52%)) rated the participant's health in the past 3 months as fair or poor (Table 4.2).

**Table 4.1: Characteristics of participants at HIV diagnosis (N=385)**

Characteristic	N (%)
Demographic	
Median (IQR) age, years	11 (8-13)
Female	199 (52%)
Clinical history	
Previous hospitalisation	105 (27%)
Attendance at PHC in past 6 months	268 (70%)
Previous TB treatment	18 (5%)
Recurrent upper respiratory tract infection	107 (28%)
Previous herpes zoster infection	41 (11%)
HIV History	
Mother or child received ART for PMTCT	5 (1%)
Circumstances leading to HIV test	
Attended PHC due to symptoms, first HIV test	323 (84%)
Previously tested but unengaged in care	19 (5%)
Attended PHC for HIV testing	43 (11%)
Likely HIV mode of acquisition	
Mother-to-child transmission	366 (95%)
Parenteral	6 (2%)
Horizontal	12 (3%)
Unknown	1 (0%)
Median (IQR) CD4, cells/mm <sup>3a</sup>	375 (215-599)
CD4 count at diagnosis, cells/mm <sup>3a</sup>	
<200	88 (23%)
200-499	162 (42%)
≥500	132 (35%)
WHO Stage	
1/2	229 (59%)
3/4	156 (41%)

<sup>a</sup> Data missing for 3 participants

#### 4.3.4.1 Respiratory

Chronic respiratory symptoms were frequent with 54% reporting cough of more than one month's duration and 16% reporting dyspnea. At rest, 12% had oxygen saturations <88% and a further 10% dropped their oxygen saturations below 88% following exercise. Of the 238 participants who underwent spirometry and were able to produce quality traces, 23 (10%) had obstructive lung function defect with only three demonstrating reversibility with salbutamol, and 43 (18%) had a reduced FVC. Notably, despite 155 (40%) screening positive for TB on the WHO screen, only one participant was found to have TB on GeneXpert testing.

**Table 4.2: Chronic morbidity in study participants**

<b>Characteristic</b>	<b>n (%) of participants</b>
Self-rated general health fair or poor in past 3 months <sup>a</sup>	197 (52%)
Fevers in the past month	162 (42%)
Diarrhoea	130 (34%)
Loss of appetite	92 (24%)
Oral candidiasis	43 (11%)
<b>Growth and Sexual development</b>	
Height-for-age z-score < -2	91 (23%)
Weight-for-age z-score < -2	106 (27%)
Head circumference-for-age z-score < -2 <sup>b</sup>	134 (35%)
Body mass index-for-age z-score < -2	62 (16%)
Delayed puberty <sup>c</sup>	18 (21%)
Non-occurrence of menarche by 15 years of age (n=17) <sup>d</sup>	4 (24%)
<b>Chronic Respiratory Disease</b>	
Chronic cough >1 month	206 (54%)
MRC Dyspnoea score $\geq 2$ <sup>e</sup>	46 (16%)
Digital clubbing	2 (0.5%)
SpO <sub>2</sub> <88% <sup>f</sup>	45 (14%)
Respiratory rate >30/min at rest <sup>g</sup>	14 (4%)
$\geq 5\%$ desaturation on exercise (n=246)	24 (10%)
FEV1 z-score, mean, sd <sup>h</sup> (n=238)	-0.73 (1.41)
FVC z-score, mean, sd <sup>h</sup> (n=238)	-0.63 (1.35)
FEF 25%-75% z-score, mean, sd <sup>h</sup> (n=238)	-0.19 (1.13)

Continued...

**Table 4.2 (continued): Chronic morbidity in study participants**

<b>Characteristic</b>	<b>n (%) of participants</b>
<b>Other chronic conditions</b>	
Gingivitis/periodontitis	11 (3%)
Visual impairment	22 (6%)
Hearing impairment	46 (12%)
Gross motor defects	2 (0.5%)
Speech impairment	4 (1%)
<b>Chronic skin disease</b>	
Any chronic skin condition	96 (25%)
Molluscum contagiosum	37 (10%)
Papular pruritic eruption	33 (9%)
Planar warts	31 (8%)
Verrucous warts	16 (4%)

<sup>a</sup> Data missing for 3 participants

<sup>b</sup> Data missing for 6 participants

<sup>c</sup> Defined as females not reaching Tanner breast stage 2 by 13 years, males not reaching Tanner testicular stage 2 by 14 years(denominator=87)

<sup>d</sup> 17 females in this age group

<sup>e</sup> Data missing for 94 participants- 60 reason unknown, 18 missed resp assessment, 14 too ill, 1 mental impairment, 1 refused

<sup>f</sup> Data missing for 58 participants-18 reason unknown, 17 too ill, 16 missed appointment, 5 equipment malfunction, 1 mental impairment, 1 refused

<sup>g</sup> Data missing for 60 participants-20 reason unknown, 17 too ill, 16 missed appointment, 5 equipment malfunction, 1 mental impairment, 1 refused

<sup>h</sup> Data missing for 147 participants- 91 uninterpretable trace, 9 missing data, 19 too ill, 11 missed appointment, 9 did not grasp technique, 8 reason unknown

#### **4.3.4.2 Growth**

The median height-for-age, weight-for-age and head circumference-for-age z-scores were -1.2 (IQR -1.9 to -0.41), -1.1 (IQR -2.1 to -0.45) and -1.4 (IQR -2.4 to -0.66) respectively. In addition, 27% of girls and 13% of boys were considered to have pubertal delay and 24% of girls aged 15 years had not experienced menarche. Of the 80 participants with WHO stage 4 disease, 66% were classified as such based on stunting alone.

#### **4.3.4.3 Other chronic morbidity**

Other chronic impairments included hearing difficulties self-reported by 12%, visual impairment by 6% and speech impairment or gross motor defects by 2%.

Chronic skin disease which included any of the following: molluscum contagiosum, papular pruritic eruption, planar warts and verrucous warts, was found in 25% of participants on examination. In addition, previous or current oral candidiasis was reported by 43 (11%), recent loss of appetite by 92 (24%) and diarrhea within the past 3 months by 130 (34%).

#### 4.3.5 Association between CD4 count and clinical conditions

Using logistic regression analysis adjusted for age and sex, participant self-report of ill-health in the past three months was associated with a CD4 count <350 cells/mm<sup>3</sup> (aOR 1.89 95% C.I 1.25-2.88) as was having a chronic skin condition (aOR 1.65 95% C.I 1.02-2.69). However, a CD4 count <350 cells/mm<sup>3</sup> or <500 cells/mm<sup>3</sup> was not associated with WHO stage, reduced FEV<sub>1</sub> or FVC z-score or growth parameters such as height-for-age, weight-for-age or head circumference z-scores (Table 4.3).

**Table 4.3: Association of clinical conditions with CD4 count at study enrolment**

	CD4 count <350 cells/mm <sup>3a</sup> (N=177)	CD4 count <350 cells/mm <sup>3</sup> aOR (95% CI)	CD4 count <500 cells/mm <sup>3</sup> (N=250)	CD4 count <500 cells/mm <sup>3</sup> aOR (95% CI)
WHO stage 3/4	77 (44%)	1.25 (0.82-1.91)	107 (43%)	1.33 (0.84- 2.10)
Self-rated general health fair /poor in past 3 months <sup>b</sup>	106 (60%)	1.89 (1.25-2.88)	137 (55%)	1.49 (0.95-2.32)
Chronic skin condition	55 (31%)	1.65 (1.02-2.69)	72 (29%)	1.61 (0.93-2.79)
Height-for-age z-score <-2	43 (24%)	0.90 (0.55-1.48)	65 (26%)	1.27 (0.73-2.19)
Weight-for-age z-score <-2	56 (32%)	1.24 (0.77-1.99)	78 (31%)	1.50 (0.88-2.56)
Head circumference-for-age z-score <-2 <sup>c</sup>	57 (32%)	0.98 (0.63-1.54)	83 (33%)	1.12 (0.70-1.82)
Pubertal delay	9 (5%)	0.68 (0.25- 1.84)	15 (6%)	1.75 (0.47- 6.50)
Visual impairment	12 (7%)	1.32 (0.54-3.23)	18 (7%)	2.43 (0.77-7.66)

Continued...

**Table 4.3 (continued): Association of clinical conditions with CD4 count at study enrolment**

	CD4 count <350 cells/mm <sup>3a</sup> (N=177)	CD4 count <350 cells/mm <sup>3</sup> aOR (95% CI)	CD4 count <500 cells/mm <sup>3</sup> (N=250)	CD4 count <500 cells/mm <sup>3</sup> aOR (95% CI)
Hearing impairment	25 (14%)	1.41 (0.75- 2.66)	33 (13%)	1.29 (0.64-2.61)
FEV <sub>1</sub> z-score <-1.64 <sup>d</sup>	32 (18%)	1.39 (0.76-2.54)	42 (17%)	1.55 (0.78-3.09)
FVC z-score <-1.64 <sup>d</sup>	25 (14%)	1.41 (0.72 -2.76)	30 (12%)	1.09 (0.52-2.28)

<sup>a,b</sup> Data missing for 3 participants, <sup>c</sup> Data missing for 6 participants, <sup>d</sup> Data missing for 147 participants -91 uninterpretable trace, 19 too ill, 11 missed respiratory assessment, 9 did not grasp technique, 9 missing data, 8 reason unknown

#### 4.4 Discussion

The main finding of this study was the heavy burden of chronic morbidity among older children and adolescents at time of HIV diagnosis. Consistent with other studies, a quarter of participants had stunting and 23% had pubertal delay (84,85,130). Although catch-up growth can be achieved after initiation of ART, children who begin treatment in later childhood are typically unable to regain their height potential (82,131). In addition, more than a third of participants had a head circumference-for-age z-score less than -2, which could partly be explained by sub-optimal brain growth in early childhood. Unlike the progressive encephalopathy, manifest as failure to attain or loss of developmental milestones or intellectual capacity and motor defects, that is typical in HIV-infected infants and young children, gross motor defects and speech impairment was rare among our participants with slow-progressive disease. However, studies have reported defects in seemingly asymptomatic HIV-infected children in fine motor function, memory, perceptual performance, quantitative abilities, and mental processing and language abilities (132,133). These deficits are subtle and are not easily identified on routine questionnaire and therefore without formative testing may have been an underrepresentation of degree of morbidity in relation to higher functioning capacity in our study. These findings have to be interpreted with caution, however, as Western references ranges for head circumference were used due to a lack of normative data from African children, and head circumference does varies by ethnic group (129).

Chronic respiratory disease was common with cough, hypoxia, reduced exercise tolerance and obstructive lung defects being the predominant features. Reversibility was rare, making asthma unlikely. Other studies have also shown a high prevalence of obstructive lung defects, with little or no reversibility (88,134). A study which performed chest computed tomography in adolescents with longstanding, vertically-acquired HIV infection showed that constrictive obliterative bronchiolitis (OB) was the predominant cause of chronic lung disease, with lymphoid interstitial pneumonitis (the most commonly recognised cause of lung disease in HIV-infected children) being a rare finding (87,88,135). OB is a progressive, life-threatening condition and is well-recognised as sequelae of respiratory tract infections, which were commonly reported by participants (136).

A quarter of all participants had chronic dermatological conditions. While not life-threatening, these are commonly recognised as stigmata of HIV infection, may take long periods to resolve following ART and for some conditions particularly planar warts, effective treatments are not available (137,138).

Importantly, no association was observed between CD4 count and WHO HIV disease stage, a finding also noted previously (139). There was also no association between CD4 count and chronic conditions, including stunting, and poor lung function. Therefore, these chronic complications develop even if immunological status is preserved. Taken together, this implies that CD4 count may not be an appropriate criterion for starting ART in older children. This also has potential implications with respect to timing of ART initiation. Based on the WHO 2013 HIV treatment guidelines, 12% of participants would not have been eligible for ART. Given the lack of evidence of the mortality benefit of immediate ART in older children and the concern about drug toxicity and adherence, guidelines until recently have recommended deferring ART in older children (9). Recent trials in adults have demonstrated that early initiation of ART reduces the risk of AIDS and non-AIDS events (90,140). However, these trials excluded older children and adolescents. Our findings demonstrate that children with slow-progressing disease may have preserved CD4 counts but do develop chronic

complications such as poor growth and chronic lung disease. It is thus possible that immediate ART may also prevent development of chronic complications in children. A randomised controlled trial would definitively establish whether immediate ART would prevent development or progression of chronic complications but this is not going to be possible given the recent change in WHO guidelines recommending immediate ART in all adults and children.

The scale-up of programs to prevent mother-to-child-HIV transmission has resulted in a substantial decline in the numbers of children infected with HIV, but coverage remains sub-optimal in many high burden countries (141). The limited availability of HIV testing services for children and the low rates of early infant diagnosis mean that for many infected infants, HIV diagnosis occurs in late childhood or adolescence following many years of ill health (142). In this study, 78% of participants had previous contact with health facilities, including 27% having been hospitalised, but had not had HIV testing. Despite recommendations that Provider Initiated Testing and Counselling should be offered as standard in health facilities in HIV high prevalence settings, in practice, HIV testing is often prompted only after presentation with typical HIV-related symptoms (143). Children with slow progressing disease may take years before they develop the well-recognised HIV indicator conditions that prompt an offer of HIV testing, by which time they develop chronic complications and organ damage which may not be reversible with ART once established. Although the majority of children were thought to have acquired HIV perinatally, for many children in the study this was their first time to have a HIV test. Although many children were orphaned, for those whose parents were accessing HIV care for their own needs, many may not have previously been advised to take their child for HIV testing. This may reflect a lack of awareness on behalf of healthcare providers of the potential for slow progressing HIV infection amongst those living with perinatally acquired HIV infection. It is also necessary to strengthen HIV testing amongst families living with HIV to ensure equal access to care for all family members.

This study also demonstrates the ability of nurses to clinically assess, diagnose and prepare children for ART initiation. Task shifting has been a key component

of ART scale up programmes in resource limited settings due to shortage of doctors (105,106). Traditionally performed for adults living with HIV or for children already initiated on ART, this study demonstrated through careful training, prompted history taking through pre designed questionnaires and development of weight-based dosing charts, CD4 monitoring at time of first clinical visit, nursing personnel were effectively able to assess and commence ART.

### ***4.5 Strengths and Limitations***

The vast majority of children were vertically-infected, implying living with HIV infection for up to 15 years without prior treatment. Participants were diagnosed after optimised PITC of attendees regardless of cause of presentation, with 80% of all attendees with previously unknown HIV status undergoing HIV testing (data not shown). The study was based in primary care facilities and therefore was not biased towards sicker children. We acknowledge several limitations. There was no HIV-uninfected or an HIV-treated comparison group in our study. Vision, hearing, neurocognitive and musculoskeletal function were not formally assessed but relied on self-report. Lung function assessment was not carried out in 5% of participants. This was partly due to logistic reasons as respiratory assessment could not be performed at the initial assessment necessitating a second appointment within two weeks which some participants did not attend. Spirometric traces could not be interpreted in 100 (26%) participants. In addition 19 (5%) participants were too ill to perform both spirometry and/or ISWT, which may have led to an underestimation of degree of lung disease present amongst the participants. Local reference ranges for lung function, puberty and head circumference are not available. British reference ranges were used for height and weight z-score calculations due to a lack of WHO weight-for-age reference ranges for children over 9 years of age, which may not be appropriate for an African population. We also acknowledge the absence of nutritional status comparators and the lack of biochemical evaluation of nutritional status of participants. Food insecurity may have played a role in findings of stunting and wasting and children found to be stunted and/or wasted

were referred to non-governmental organisations in their locality for assessment of eligibility for food aid.

#### **4.6 Conclusion**

This study shows a substantial burden of chronic morbidity among HIV-infected children diagnosed in later childhood, even among those with preserved CD4 counts. Recognition of this burden is needed to stimulate earlier diagnosis and improve access to HIV care for this age group.

There is a pressing need to strengthen PITC and potentially provide other more effective services for HIV testing in this age group, and for timely institution of ART. Previous recommendations of deferred ART in children may have put children at risk of developing chronic complications. The recent WHO guidelines recommending treatment of all HIV-infected individuals regardless of age and disease stage, may reduce the risk of development of chronic complications (117). Studies investigating the impact of immediate ART on AIDS and non-AIDS events in children and the pathogenesis of chronic complications will inform development of optimum care provision for HIV-infected children.

## **5. Caregiving arrangements for and HIV status disclosure to children diagnosed with HIV infection**

### ***5.1 Background***

The high mortality rates associated with the early adult epidemic of HIV in sub-Saharan Africa has seen high numbers of children left orphaned in the region. In Zimbabwe in 2015 there were an estimated 450,000 children aged 0-17 years orphaned due to HIV (144). Many of those orphaned due to parental HIV are also living with HIV and are being cared for by extended family members. Even for children who have one or both parents alive, economic hardships in the region, particularly in Zimbabwe since 2000, have resulted in many adults seeking work in neighbouring countries, leaving their children in the care of extended family members (145). Therefore, in the context of a southern African family, the caregiver of a child may not always a parent.

Children's ability to engage effectively in ART programmes depends on their caregiver's willingness to engage and be supportive of the child in their care, without which, children's outcomes will suffer (146). Caregivers are critical in helping children access services, take their treatment and to help them understand the consequences and implications of living with HIV, a non-curable and potentially fatal illness. A critical step to facilitating this is disclosing to a child his or her HIV status (147). The importance of engaging caregivers in the disclosure process cannot be understated (148,149). Children's and adolescent's knowledge of their HIV status has been shown to be associated with improved adherence to ART and a higher rate of retention in care (150). The WHO recommends that partial disclosure begins from the age of 6-7 years and that by adolescence, youth should know their status (151).

Despite the importance of disclosure, several studies have shown that disclosure of HIV status to children and adolescents is often delayed. In a cross sectional study of disclosure to children in 6-14 year age group in Kenya, the overall prevalence of disclosure was 26% (152). It was noted that as age of the child increased so did disclosure rates. Tadesse et al in a cross sectional study in

Ethiopia of children with a mean age of 10 years attending for HIV care, found only one- third of children were aware of their status (153).

A repeated reason cited by caregivers for not disclosing a child's HIV status is fear of discrimination for the child and the family and as a consequence of disclosure an unmasking of the parents HIV status (154,155). Discussion surrounding HIV infection can then become very limited and become a taboo topic. If HIV cannot be discussed openly in households then school teachers who can serve as a conduit of knowledge for children, will face challenges in their roles as educators.

The aim of this study was to investigate the socio demographic features of the cohort of children in our study, in particular the caregiving arrangements, schooling and disclosure of HIV status to children, and the association of caregiving arrangements and other socio-demographic factors with non-disclosure following a child's HIV diagnosis.

### **5.2 Methods**

#### **5.2.1 Data collection**

This study was conducted among children aged 6-15 years, recruited as described in chapter 3. The research question of disclosure amongst participants arose on the MD candidates review of data collected through the course of the study. Questionnaires were designed to determine whether or not disclosure had taken place to the children at the time of study enrolment. This was to determine whether or not discussion had taken place surrounding HIV testing between caregiver and child and also to ensure accidental disclosure to the child did not take place during initial assessment, which could lead to distress on behalf of the child.

A caregiver was defined as an adult aged 18 years and over, responsible for a child's daily care. Caregivers were informed of a child's HIV test result at the time of testing. Discussion of the HIV test result with the child was undertaken by the healthcare provider in the presence of the caregiver, but only with the caregiver's consent.

At the initial assessment following diagnosis, a nurse-administered questionnaire was administered to the child's caregiver. This consisted of a detailed socio-demographic history including guardianship, orphanhood status, and current enrolment and attendance at school. The assessment took place within a week of the child's HIV diagnosis. In addition, the current and past caregiving arrangements of the child was ascertained i.e. whom they had lived with since birth. The reason for any change in caregiver was also recorded.

Caregivers were asked if the HIV status of the child's biological parents were known to them. They were also asked whether they had told their child the results of the HIV test performed on the child. If the child had not been disclosed to, the reasons for non-disclosure were recorded using a pre-defined checklist as well as an open-ended question. In addition, a child's awareness of his/her parents' and siblings' HIV status was documented.

Caregivers were also asked about the knowledge of the child's HIV status within the extended family (e.g. siblings, other family members), as well as outside of the family i.e. to friends of the family, school teacher and principal (if child attending school) and church pastor (if a church goer).

### **5.2.2 Analysis**

The frequency of reasons for non-disclosure was calculated. The association between *a priori* defined variables: age, gender, orphanhood status, having had a change in caregiver since birth, type of caregiver, awareness of parents' HIV status, any parent taking ART, WHO stage, interruption in schooling in the past 3 months and recent diagnosis of HIV infection and non-disclosure of HIV status to the child was determined using univariate analysis, followed by a multivariate logistic regression model, to control for confounders. Age was chosen *a priori* to determine whether older children were more likely to be disclosed to than younger children. A p-value of less than 0.05 was considered statistically significant.

## **5.3 Results**

### **5.3.1 Sociodemographic characteristics**

#### **5.3.1.1 Caregiving status**

Of the 385 children enrolled nearly 60% of children were single (one parent deceased) or double orphans (both parents deceased). More than 40% of children had a non-parent as the current primary caregiver (Table 5.1). The most common non-parental caregiver was an aunt or uncle (n= 79, 48%) followed by a grandparent (n=61, 37%). Notably, 30% of children whose mother and/or father were alive lived with a non-parent caregiver. Caregiving arrangements were fluid and 57% of children had a change in caregiver since birth (43% having one change in caregiver, 13% having two changes in caregiver and 1% having three changes in caregiver). The main reason for change in caregiver was due to death of the child's primary caregiver (n=126, 57%).

#### **5.3.1.2 Schooling**

School enrolment rates were high, with 351 children currently enrolled in school, although nearly a quarter of children had missed a week or more of school in the past three months, predominantly due to illness (Table 5.1).

#### **5.3.1.3 HIV in the family**

The HIV status of 268 (70%) mothers and 190 (49%) fathers (either alive or deceased) was known to the respondent. One hundred and forty (36%) respondents reported that both the child's parents were living with HIV. Two hundred and four (53%) children had a parent who was on ART. Of the 250 (65%) mothers and 172 (45%) fathers whose HIV status was reported as positive by the respondent, the child was aware of their mother's HIV positive status in 41% of cases and father's HIV positive status in 38% of cases. Three hundred and forty five participants had 1 or more natural sibling, 51 of whom were known by the caregiver to be HIV-infected (35 were still alive, 16 had died) and 37 were currently or had previously been on ART. Children were aware of their siblings' HIV-positive status in 45% of cases.

**Table 5.1 Sociodemographics and HIV history within the family**

Variable	N=385(%)
<b>Orphanhood</b>	
Both parents alive	157 (41%)
Maternal Orphan <sup>1</sup>	150 (39%)
Paternal Orphan <sup>2</sup>	130 (34%)
Double Orphan	58 (15%)
<b>Current caregiver</b>	
Biological parent	220 (57%)
Nonparent Caregiver	165 (43%)
Aunt/Uncle	79 (48%)
Grandparent	61 (37%)
Sibling	17 (4%)
Other relative	4 (1%)
Institution	4 (1%)
<b>Currently enrolled in school</b>	351 (91%)
<b>Missed ≥5 days school in past 3 months<sup>3</sup></b>	80 (23%)
- because of illness	61 (76%)
- financial reasons	10 (13%)
- other reason (relocation, death in family, teachers strike)	5 (5%)
- no reason given	4 (1%)
<b>HIV within the family<sup>4</sup> (alive or dead)</b>	
Both parents HIV+	140 (36%)
Mother HIV+	250 (65%)
Father HIV+	172 (45%)
One or more natural sibling HIV+ <sup>5</sup>	51 (13%)

<sup>1</sup> Mother alive/dead/unknown by n=3

<sup>2</sup> Father alive/dead/unknown by n=19

<sup>3</sup> Data missing for n=4,

<sup>4</sup> 117 and 195 responders did not know mother's and father's HIV status respectively

<sup>5</sup> 123 respondents did not know child's siblings' HIV status

### 5.3.4 HIV status disclosure

Disclosure of HIV status had been made to 202 (52%) children, with a higher proportion of 11 to 15 year olds than 6 to 10 year olds aware of their HIV diagnosis (79% vs. 19%) (Table 5.2). Disclosure to siblings and extended family members had occurred in 31% and 63%, respectively. Disclosure to individuals outside the family occurred infrequently (i.e. friends of family (n=26), school teacher (n=27), school headmaster (n=13), church pastor (n=24).

**Table 5.2: Reasons for non-disclosure (multiple reasons accepted)**

	<b>Total n=385</b>	<b>6-10 years n=185</b>	<b>11-15 years n=200</b>
HIV status not disclosed to child by caregiver	183 (48%)	146 (79%)	37 (19%)
Child too young	112 (62%)	100 (68%)	12 (32%)
Child doesn't understand	102 (56%)	86 (59%)	16 (43%)
May tell others his status	48 (26%)	39 (27%)	9 (24%)
May hurt the child to know his status	14 (8%)	5 (3%)	9 (24%)
Counsellor should disclose to child	10 (5%)	3 (2%)	7 (19%)
I don't know how to disclose to child	10 (5%)	6 (4%)	4 (11%)
Another relative should disclose to the child	8 (4%)	4 (3%)	4 (11%)
Child is not sick	2 (1%)	2 (1%)	0 (0%)
Child is too sick	2 (1%)	2 (1%)	0 (0%)

n=11 no reason given

## **5.4 Discussion**

### **5.4.1 Living Arrangements**

This study highlights unstable living arrangements for children infected with HIV, with frequent change of caregiver in their young lives, most often but not exclusively due to parental death. As expected, there was a high prevalence of orphanhood (156). More than a third of caregivers were grandparents, who are left to care for grandchildren following the death of their own children from HIV. A study from Zimbabwe highlighted the difficulties faced by elderly guardians caring for children with HIV, including a lack of HIV treatment literacy leading to children being unsupported in HIV care (157). Change in caregiving arrangements may interrupt children's engagement with HIV care due to movement of dwelling and thus change in the clinic where the child is accessing HIV care.

### **5.4.2 Discussion of HIV within families**

A key finding of this study is that caregivers of children living with HIV have difficulty in discussing HIV with the child in their care. This resulted in high rates of non-disclosure to children at time of HIV diagnosis, particularly among the 6-10 year olds (79% were not disclosed to). Caregivers play a central role in not

## Chapter 5. Caregiving arrangements

only having discussions about HIV with their children but also facilitating disclosure and post-disclosure discussions between children and health care providers. WHO recommends that disclosure discussion begins from the age of 6 years with age-appropriate discussions (151). Despite the fact that 83% of the children had one or both parents on ART, caregivers had not broached the subject of HIV, fearing the child was too young to understand. Perceived stigma and wanting to protect children from their diagnosis have been reasons reported previously for non-disclosure (158). However, older children who learn their status, recall that the initial feeling of shock and sadness at time of disclosure is relatively short-lived and believe they are in a stronger position to engage in ancillary support groups and be in control of their health after disclosure (159,160).

Females were more likely to be disclosed to than males reflecting potentially that girls are deemed to be more mature. Girls have sexual debut earlier than males in this setting, and perhaps caregivers hoped to prevent onward transmission of HIV (161,162).

Discussion of HIV within the family was not common place in general. The majority of participants were perinatally-infected (see chapter 3), but only 33% were aware of their parents' HIV status. While type of caregiver (i.e. parent vs. non parent) was not associated with disclosure of HIV status to the child, children who were not aware of their parents' HIV status were also less likely to have been told about their own HIV-status. This highlights the general culture of silence surrounding HIV within family structures. Many children living with HIV have experienced the trauma and grief of family members dying including siblings and parents (98). Households can be fractured due to high rates of orphanhood and frequent change of caregiver. Not discussing with a child their HIV status or HIV status of their parents/caregivers will potentially create further fracturing of relationships creating issues of trust between children and their guardians. Previous studies have highlighted the fear that discussion of children's HIV status will unmask parents HIV status and parents fear blame will be assigned to them for transmission (154,155,163).

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Few children's HIV status had been discussed by caregiver outside of the family which reflects the perceived stigma that is associated with living with HIV and perhaps a desire to protect the child from such stigma (159,164). Children often feel they receive minimal information about HIV from healthcare providers and their caregivers and the culture of silence surrounding HIV can leave them with many questions (165). While disclosure, which often amounts to naming the diagnosis only, is done by healthcare workers, caregivers are reluctant to continue the discussion outside of the clinic setting (149).

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**Table 5.3 Risk factors for non-disclosure**

	<b>n Not disclosed to / Total</b>	<b>Uni-variate OR</b>	<b>p-value</b>	<b>Multi-variate OR</b>	<b>p-value</b>
<b>Age</b>					
6-10y	149/185 (79%)	16.5 (10.0-27.25)	<0.001	18.89 (10.64-33.55)	<0.001
≥11y	37/200 (18%)	1			
<b>Sex</b>					
Female	81/199 (41%)	0.57 (0.38-0.85)	0.006	0.39 (0.22-0.67)	0.001
Male	102/186 (55%)	1			
<b>Orphanhood Status</b>					
Non-orphan	99/161 (61%)	2.62 (1.73-3.98)	<0.001	1.50 (0.82-2.76)	0.19
Maternal and/or Paternal Orphan	84/222 (38%)	1			
<b>Change of caregiver since birth</b>					
No previous caregiver change	90/162 (55%)	1.75 (1.16-2.64)	0.008	1.00 (0.47-2.10)	0.99
≥1 change of caregiver	90/216 (42%)	1			
<b>Current Caregiver</b>					
Parent caregiver	114/220 (52%)	1.50 (1.0-2.25)	0.052	1.01 (0.47-2.16)	0.97
Non-parent caregiver	69/165 (42%)	1			
<b>Disclosure of parents' HIV status to child</b>					
Unaware of parents' HIV status	171/260 (66%)	18.1 (9.47-34.58)	<0.001	32.42 (13.19-79.71)	<0.001
Awareness of parents' HIV status	12/125 (10%)	1			
<b>Parent taking ART</b>					
Mother/Father not on ART	93/189 (49%)	1.14 (0.76-1.70)	0.52	1.64(0.90-2.98)	0.10
Mother/Father on ART	90/196 (46%)	1			

Continued...

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**Table 5.3 (continued) Risk factors for non-disclosure**

	<b>n Not disclosed to / Total</b>	<b>Uni-variate OR</b>	<b>p-value</b>	<b>Multi-variate OR</b>	<b>p-value</b>
<b>WHO STAGE</b>					
1/2	113/229 (49%)	1.20 (0.8-1.80)	0.39	1.28 (0.74-2.22)	0.37
3/4	70/156 (45%)	1			
<b>Schooling</b>					
Uninterrupted schooling in the last 3 months	132/271 (49%)	1.35 (0.82-2.24)	0.24	1.15 (0.58-2.26)	0.68
Interrupted Schooling in the last 3 months	33/80 (41%)	1			
<b>Time of diagnosis</b>					
Newly diagnosed	149/299 (50%)	1.81 (1.08 - 3.02)	0.02	2.52 (1.29- 4.91)	0.007
Previously diagnosed	28/79 (35%)	1			

### **5.5 Limitations of the study**

A limitation of our findings is that this a cross sectional analysis and so only provides a snapshot of disclosure at time of diagnosis. Further qualitative work may have helped to further tease out reasons for non-disclosure by caregivers. Interviews with healthcare providers may have provided insight into their views and perceived barriers to disclosure. This study was conducted soon after diagnosis and it may have been an early time point to begin the disclosure process with young children given what is already known about caregiver's hesitancy to begin disclosure discussions. Children were not directly asked what they understood as to what testing had been performed and so there was a reliance on caregivers recall and potential desire to appease the interviewer may have been present.

### **5.6 Conclusion**

It is important for programme providers to be mindful of challenges for children in this high prevalence setting of change in caregiver/household and orphanhood rates amongst this age group. Such situations may provide a challenge to accessing ART due to change in location of household but also the emotional challenges of coping with life through loss of a parent and growing up with HIV (115).

Disclosure is not just a single event in life but an ongoing process – particularly for younger children which must start at an age appropriate understanding and be escalated over time (148,149,164,166). As children grow into adolescents their knowledge of their HIV status should enable them to adhere to treatment and also decide how and when they will onwardly disclose to their peers and their sexual partners as they get older.

Caregivers need to be equipped with the skills and support to be able to discuss HIV within their family unit openly and honestly in a way that is understandable to children (167). It is likely caregivers feel they lack knowledge on how to answer potential questions that may arise from such a discussion e.g. regarding

## Chapter 5. Caregiving arrangements

mode of acquisition, onward transmission, coping with stigma, schooling and sexual relationships (158). Education is needed for caregivers to guide them on how to discuss HIV amongst their family unit in a way an open and honest forum that is understandable to their children. It would be assumed that healthcare providers would provide this support. However, healthcare workers may themselves lack the skills to discuss a child's HIV diagnosis and may lack culturally appropriate methods (167,168)

Use of disclosure tools will aid in helping caregivers discuss HIV with their child (166,167). Active engagement between health care provider and caregiver can help both parties understand the potential barriers to disclosure and help them come to a solution together.

It is essential that HIV care programmes are all encompassing involving the family unit as a whole and not just focusing on ART provision. Open discussion of HIV status amongst family members and support of such family members is vital. As we move towards the 90-90-90 targets, we have a responsibility towards children and adolescents of today to inform them of their HIV status so as to empower them to be in control of their own status and future (1).

## **6. Clinical outcomes among in children and adolescents accessing decentralised HIV care**

### **6.1 Introduction**

By 2015, an estimated 1.8 million children under 15 years of age were living with HIV globally, the majority in Sub-Saharan Africa, yet just half were accessing ART (169). While the number accessing HIV treatment represents gains from 2010 (49% of all children infected were accessing ART in 2015 as compared to just 21% in 2010), children lag disproportionately behind adults in terms of ART coverage (169).

As ART programmes have scaled up, the major barriers to ART access have been the lack of healthcare professionals to provide HIV care, overcrowding of clinics and distance to facilities where such care is available (100,170–173). Among adults, the increase in numbers of individuals accessing ART has led to decentralisation of HIV care provision from secondary to primary health care facilities, and task-sharing to involve nurses in treatment of HIV infection (174,175). The aims of decentralisation and task-sharing are to improve access to care for patients and relieve pressure on heavily overburdened secondary care facilities (176). More recently, differentiated care initiatives are focusing on providing services which are more client focused and tailored to specific needs of diverse populations of people living with HIV including children and adolescents (177). Zimbabwe has incorporated the concept of differentiated care into its recent HIV treatment framework (178).

Clinical outcomes among adults HIV care in nurse-led decentralised programmes have been comparable to those in secondary healthcare facilities (174,175,179,180). Provision of HIV care to children and adolescents is associated with additional complexities, which may impact on clinical outcomes (176). These include reliance on guardians, who are often not biological parents, for access to and retention in care, weight-based ART dosing, difficulties in discussing HIV and disclosing HIV status to children (96,149,150). Older children and adolescents with HIV have higher rates of virological failure and attrition

than adults (181,182). These factors have led to a relative reluctance by primary care level providers to provide HIV care to this age-group (183). WHO guidelines now recommend “treat all” living with HIV and Zimbabwe, since 2016, has adapted its national guidelines to reflect this. Limited data are available on ART care provision to children by nurses in primary health care facilities (184).

This study investigated clinical outcomes among children and adolescents accessing decentralised HIV care services provided by nurses in Harare, Zimbabwe.

## **6.2 Methods**

### **6.2.1 Study Setting**

A prospective cohort study of children aged 6-15 years was conducted in seven primary healthcare clinics (PHCs) in south west Harare, Zimbabwe between January 2013 and June 2016. This chapter reports the results of the cohort enrolled as per chapter 3 of this thesis. Children and adolescents found to be HIV positive were followed for 18 months from time of study enrolment. Clinics where the study was performed were providing nurse-led HIV care to adults as per Zimbabwe national guidelines but had not been treating children living with HIV. Research nurses based at each clinic were trained on paediatric HIV testing and counselling and provision of HIV care, treatment monitoring and management of infections, based on the Integrated Management of Childhood Illness (IMCI) algorithm, over a 2 week period prior to study commencement (119). The Ministry of Health and Child Care training tools were utilised and simple ART dosing charts were produced to facilitate weight-based dosing. Criteria for referral to secondary level facilities were pre-defined, including “danger signs” based on the IMCI algorithm. Nurses carried out ART eligibility screening, initiated ART and provided follow-up care, supported by weekly visits from a physician. Adherence counselling was provided by primary care counsellors trained in paediatric HIV care. On completion of study follow up, HIV care and management was transferred to clinic nursing staff. Nurses in the

employ of the clinic worked together with research nurses and were trained on HIV care and management for children over the duration of the study.

### **6.2.2 Participants**

Children aged between 6 to 15 years who tested HIV-positive through provider-initiated HIV testing and counselling were enrolled into the cohort study as described in Chapter 3. A proportion (44%) were simultaneously enrolled into a randomised controlled trial to assess impact of household support to children living with HIV on virological outcomes [trial registry number PACTR201212000442288] (185). Such participants received an intervention of household visits timed to follow on from clinic visits. Such visits were carried out by a trained volunteer community support worker. The support worker addressed issues of disclosure, ART side effects and the importance of adherence. They also helped to assist caregivers in social welfare issues such as accessing support for school fees and advising on testing of household members for HIV.

### **6.2.3 Study procedures**

At the initial assessment visit within a week of HIV diagnosis, socio-demographic data, past clinical history and current symptoms were assessed, and a standardised examination performed, as described in chapter 3. Participants were seen within two weeks of the initial visit to assess adherence and determine side effects of cotrimoxazole, and to commence ART if eligible. The schedule for follow-up was based on national guidelines, with visits at two and six weeks post ART commencement and then on a three-monthly basis. Participants not eligible for ART at baseline underwent a three-monthly symptom-based review and examination to reassess ART eligibility. At each visit, a standard proforma was used to collect information on current symptoms including TB symptom screen, side effects of ART, history of contact with primary healthcare and hospitalisation since the previous visit (confirmed by patient-held records) and history of incident infections. CD4 count was performed 6 monthly for all participants. HIV viral load testing was performed at 48 weeks post ART commencement, using COBAS Ampliprep/Taqman 48 Version 2.0.

#### **6.2.4 Definition of outcomes**

Unscheduled visits were defined as visits occurring outside the scheduled visits for either a medical or non-medical reason (e.g. counselling). Side effects were graded according to the DAIDS grading system (186). Hospitalisation was defined as a participant spending one night or more in a hospital. If a participant had more than one hospitalisation they were counted separately even if related to the same clinical issue. Transfer out was defined as a caregiver informing the clinic of the participant changing care to another clinic and a transfer letter being provided. Participants who failed to attend more than two scheduled appointments were traced through a phone call and/or a home visit. Participants were defined as having moved away if they had moved care to another clinic without informing clinic staff. Participants were deemed lost to follow-up (LTFU) if they could not be traced. Tracing was performed at clinic level by research nurses who phoned the participant's guardian on 2 occasions if a participant had not returned for a visit within 3 months of the scheduled date. If after the second phone call a participant could not be reached then a community health worker visited the house. If a participant died the cause of death was determined through hospital records. In the case of death occurring outside of hospital this was confirmed through verbal autopsy with the caregiver.

#### **6.2.5 Data analysis**

Rates of hospitalisation, unscheduled visits and death were calculated. Cox proportional modelling was used to determine the hazard of death, unscheduled visits and hospitalisation, controlling for factors found to be significantly associated with the outcome i.e.  $p$  value  $<0.05$ , in univariate analysis.

### **6.3 Results**

#### **6.3.1 ART commencement**

A total of 385 participants were enrolled into the study and provided 450 person years of follow-up and a median of 504 days per participant (IQR 1-515). Over the 18 month period, 296 (77%) participants commenced ART, 70% of whom did so within 4 weeks of enrolment. Of the 89 participants who did not initiate ART,

7 were eligible according to national guidelines and 82 were not eligible during follow-up. The median number of days on ART for those who initiated ART over the study was 485 (IQR 359-495) days.

### 6.3.2 Retention in Care

At the end of 18 months, 286 (74%) were still in care, 50 (13%) had transferred to another clinic, 12 (3%) moved to another clinic without informing clinic staff, 9(2%) moved away and did not transfer to another clinic, 13 (3%) died, 1 withdrew from the study after initial assessment and 14 (4%) were lost to follow up (Table 6.1). Importantly, those who did not start ART were significantly more likely to be lost to follow-up than those who started ART ( $p<0.001$ ).

**Table 6.1: Outcomes at 18 months of cohort participants by ART initiation status**

	Total N=385	Initiated ART over follow up period N=296	Did not initiate ART over follow up period N=89	P- value
In care to end of study follow up	286 (74.3%)	243 (82.1%)	43 (48.3%)	<0.01
Planned transferred to another clinic	50 (13.0%)	30 (10.1%)	20 (22.5%)	<0.01
*Left area without transfer of care	9 (2.3%)	2 (0.7%)	7 (7.9%)	<0.01
*Not in care and untraceable	14 (3.6%)	6 (2.0%)	8 (9.0%)	<0.01
No planned transfer, but was found in care at another clinic	12 (3.1%)	3 (1.0)	9 (10.1)	<0.01
Withdrew from study	1 (0.3%)	0 (0.0%)	1 (1%)	0.06
Died	13 (3.4%)	12 (4.1%)	1 (1%)	0.18

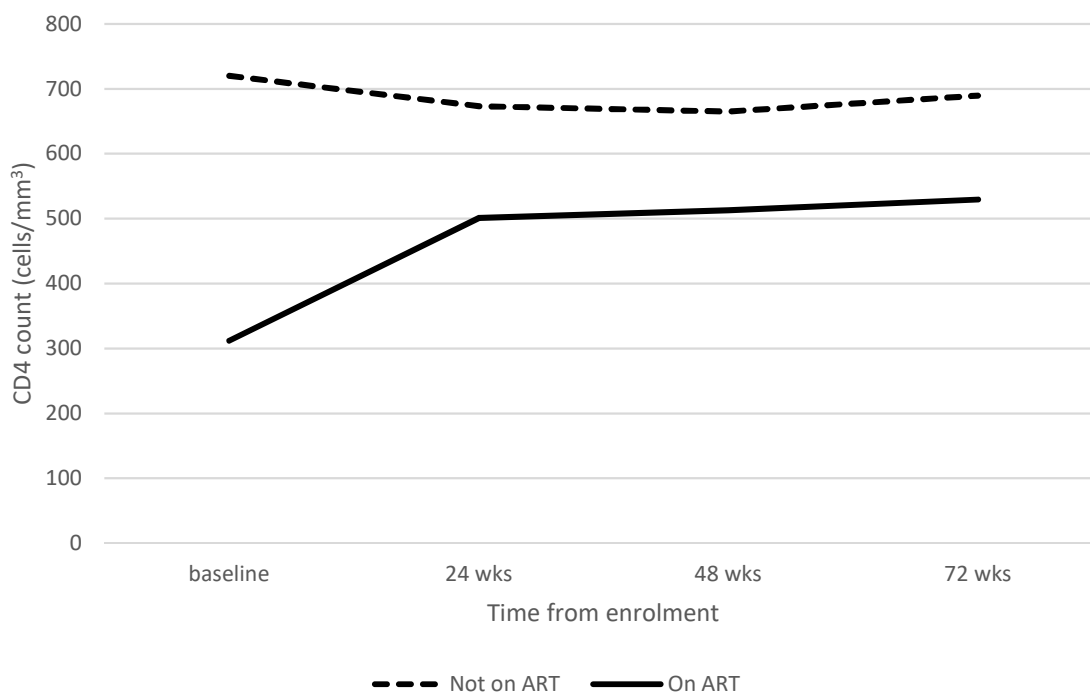
\*ascertained through phone calls and home visits

### 6.3.3 Immunological and virological outcomes

CD4 counts for those who commenced ART increased over the follow-up period, with those who did not start ART (n=89) maintaining their CD4 counts (Figure 6.1). Of those who commenced ART within 24 weeks of enrolment into the study

(n=273), 200 had a viral load sample collected between 40-72 weeks post ART, with 195 results obtained. 124 (64%) of those whose viral load result was obtained had a viral load <400 copies/ml.

**Figure 6.1: Median CD4 count over 18 month follow up by ART status**



### 6.3.4 Unscheduled Visits

There were 146 unscheduled visits made by 99 participants over the follow-up period, equivalent to a rate of 34.94/100 person years (95% CI 29.70- 41.09). Ten unscheduled visits resulted in hospitalisation, all of whom were receiving ART. The most common reason for an unscheduled attendance to the clinic was illness (n=133, 91%). Other reasons included medication collection (n=5, 3%) and additional adherence counselling (n=8, 6%). The major cause of illness leading to an unscheduled visit was respiratory tract infection (responsible for 45% of unscheduled visits due to illness), followed by skin infections which accounted for 22% of unscheduled visits due to illness (Table 6.2).

Side-effects from ART resulted in unscheduled visits in 20 patients (15% of unscheduled visits due to illness). Of these, Grade 1 nevirapine hypersensitivity was the most common side-effect (n=8). Only one participant was hospitalised

due to ART side effects- for rehydration secondary to grade 3 vomiting. Other ART side effects reported at routine 3 monthly follow up were uncommon and self-limiting-consisting of nausea (6%), vomiting (6%), abdominal pain (3%), diarrhoea (6%), fatigue (5%), rash (3%), jaundice (0.1%), dizziness (3%) vivid dreams (2%), and confusion (1%). Overall, side effects of ART resulted in drug switches in 11 cases (n=9 due to nevirapine hypersensitivity, n=1 anaemia due to zidovudine and n=1 grade 3 efavirenz hypersensitivity reaction). Such switches were managed in the primary care clinics by nursing staff with consultation from the study physician.

**Table 6.2: Reasons for unscheduled visits due to illness (n=133)**

<b>Cause of unscheduled attendance</b>	<b>N (%)</b>
<b>Respiratory tract infection</b>	60 (45%)
Upper respiratory tract infection	27
Lower respiratory tract infection	16
Pulmonary TB	11
Otitis Media	2
Tonsillitis	4
<b>Skin infections</b>	29 (22%)
Oro-labial Herpes Simplex	5
Herpes Zoster	5
Chicken Pox	1
Bacterial skin infection	15
Fungal skin infection (Tinea capitis or corporis)	2
Papular pruritic eruption	1
<b>Gastrointestinal disease</b>	16 (12%)
Gastroenteritis	9
Chronic diarrhoea	2
Hepatitis A	1
Oral candidiasis	3
Oesophageal candidiasis	1
<b>Antiretroviral therapy side effects</b>	20 (15%)
Grade 1 Nevirapine Hypersensitivity	8
Grade 2/3 NNRTI Skin hypersensitivity	8
Grade 2/3 vomiting	3
Anaemia	1

Continued...

**Table 6.2 (continued): Reasons for unscheduled visits due to illness (n=133)**

Cause of unscheduled attendance	N (%)
<b>Miscellaneous</b>	8 (6%)
Minor trauma	1
Gingivitis	2
Conjunctivitis	2
Mumps	1
TB lymphadenitis	2

### 6.3.5 Hospitalisations

There were 34 hospitalisations in 27 participants, 9 of which resulted in death. The rate of hospitalisation was 8.14/100 person years (95% CI 5.81- 11.39). Lower respiratory tract disease was the commonest reason for admission (Table 6.3). TB was the cause of hospitalisation in 8 participants diagnosed through sputum testing using GeneXpert or based on chest X-ray findings. Six participants were hospitalised more than once for the same clinical diagnosis (1 admitted twice for HIV related anaemia, 1 admitted twice for lower respiratory tract infection, 1 admitted twice for Steven Johnson's syndrome secondary to cotrimoxazole due to ongoing symptoms, and 1 admitted thrice for recurrent lower respiratory tract infection). Two participants were admitted twice but for different clinical events. Only three hospitalisations occurred in participants not taking ART, two of which were due to malaria. Only one was HIV-related, namely HIV-associated anaemia and thrombocytopenia, and resulted in death. The CD4 count at hospitalisation in this participant was 1114 cells/mm<sup>3</sup>.

### 6.3.6 Deaths

The mortality rate was 2.86 /100 person years (95% CI 1.65-4.95). Of the 13 deaths in the cohort, 12 occurred in hospital and respiratory disease was the most common cause (Table 6.4). The median CD4 count at enrolment of those who died was 73 cells/mm<sup>3</sup> (IQR 12-205) and 77% of those who died had WHO Stage 3 or 4 disease at enrolment. The median time from enrolment to death was 76 days (IQR 59-410).

**Table 6.3: Causes of hospitalisation (n=34)**

Cause of hospitalisation	N (%)
<b>Respiratory Illness</b>	n=18 (53%)
Pulmonary TB	7
Disseminated TB	1
Lower Respiratory Tract Infection	9
Pneumocystis jiroveci Pneumonia	1
<b>Neurological Illness</b>	n=5 (15%)
Bacterial Meningitis	1
Cryptococcal Meningitis	2
CNS Lymphoma	1
Seizure (cause unknown)	1
<b>Miscellaneous</b>	n=11 (32%)
Hyperglycemia	1
Anemia <sup>a</sup>	3
Congestive Cardiac Failure	1
Gastroenteritis	1
Vomiting Secondary to ART	1
Malaria <sup>b</sup>	2
Stevens Johnson Syndrome Secondary to cotrimoxazole	2

Numbers refer to hospitalisation events rather than numbers of participants admitted, <sup>a</sup>n=1 not on ART, <sup>b</sup>n=2 not on ART

**Table 6.4: Causes of death amongst cohort participants over 18 month follow up (n=13)**

Cause of death	n (%)
Pulmonary TB	4 (31)
Lower respiratory tract infection	4 (31)
Malignancy- CNS Lymphoma	1 (7)
Congestive Cardiac Failure	1 (7)
Meningitis	1 (7)
Accidental Drowning	1 (7)
Anaemia/Thrombocytopenia	1 (7)

### 6.3.7 Hazards for unscheduled visits, hospitalisation and death

A CD4 count less than 350cells/mm<sup>3</sup> at enrolment, WHO stage 3 or 4 HIV disease and wasting were associated with hospitalisation and death in univariate analysis (Table 6.5). CD4 count less than 350cells/mm<sup>3</sup> and advanced WHO stage remained significantly associated with the outcome in multivariate analysis for

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hazard of hospitalisation (aHR 3.6 (95%CI 1.6-8.2) for CD4 count, and aHR 2.6 (95% CI 1.1-6.2) for WHO stage, but no variables remained significantly associated with the hazard of death. Being older (HR 2.1 (95%CI 1.4-3.1), WHO stage 3 or 4 disease (HR 1.5 (95% CI 1.0-2.1) and wasting (HR 1.8 (95% CI 1.3-2.7)) were associated with having unscheduled visits due to illness. On multivariate analysis, association with older age (aHR 1.9 (95%CI 1.3-3.1)) and wasting (aHR 1.8(95%CI 1.0-2.3)) remained significant.

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**Table 6.5: Cox proportional Hazard Ratio for hospitalisation, unscheduled visit due to illness and death**

		Hospitalisation N=34					Unscheduled visit N=118				Death N=13			
		Total	N	Rate (95% CI)	Crude hazard Ratio	AHR*	N	Rate (95% CI)	Crude hazard Ratio	AHR*	N	Rate (95% CI)	Crude hazard Ratio	AHR*
<b>Age</b>	<b>11-15</b>	200	17	7.7 (4.8-12.5)	0.9 (0.5-1.8)	-	82	37.3 (30.1-46.4)	2.1 (1.4-3.1)	1.9 (1.3-2.9)	7	3.0 (1.4-6.2)	1.1 (0.4-3.3)	-
	<b>6-10</b>	185	17	8.6 (5.3-13.8)	1	-	36	18.2 (13.1-25.2)	1	-	6	2.8 (1.2-6.1)	1	-
<b>Sex</b>	<b>Female</b>	199	15	6.9 (4.2-11.5)	0.7 (0.4-1.4)	-	68	31.4 (24.7-39.8)	1.3 (0.9-1.8)	-	9	3.8 (2.0-7.4)	1.6 (0.5-5.5)	-
	<b>Male</b>	186	19	9.44 (6.0-14.8)	1	-	50	24.9 (18.8-32.8)	1	-	4	1.8 (0.68-4.9)	1	-
<b>CD4 at enrolment a</b>	<b>&lt;350</b>	177	26	13.1 (8.9-19.3)	4.1 (1.8-9.4)	3.6 (1.6-8.3)	65	32.8 (25.7-41.8)	1.4 (0.9-1.9)	-	11	5.2 (2.9-9.3)	5.0 (1.1-23.1)	4.2 (0.9-19.8)
	<b>&gt;350</b>	205	7	3.2 (1.5-6.8)	1	-	53	24.5 (18.7-32.0)	1	-	2	0.8 (0.2-3.4)	1	-
<b>WHO stage</b>	<b>3-4</b>	155	25	14.8 (10.0- 21.9)	4.0 (1.9-8.6)	2.6 (1.1-6.2)	59	34.9 (27.1-45.1)	1.5 (1.0-2.1)	1.2 (0.8-1.9)	10	5.4 (2.9-10.0)	4.1 (1.1-15.2)	2.5 (0.6-10.7)
	<b>1-2</b>	230	9	3.6 (1.9-6.9)	1	-	59	23.7 (18.4-30.6)	1	-	3	1.1 (0.3-3.5)	1	-
<b>ART within 4 weeks</b>	<b>Y</b>	206	22	9.2 (6.1-14.0)	1.4 (0.7-2.9)	-	69	28.9 (22.8-36.5)	1.1 (0.75-1.6)	-	10	3.9 (2.1-7.3)	2.1 (0.6-7.9)	-
	<b>N</b>	179	12	6.7 (3.8-11.8)	1	-	49	27.3 (20.0-36.6)	1	-	3	1.5 (0.5-4.7)	1	-

Continued...

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**Table 6.5 Continued: Cox proportional Hazard Ratio for hospitalisation, unscheduled visit due to illness and death**

		Hospitalisation N=34					Unscheduled visit N=118				Death N=13			
		Total	N	Rate (95% CI)	Crude hazard Ratio	AHR*	N	Rate (95% CI)	Crude hazard Ratio	AHR*	N	Rate (95% CI)	Crude hazard Ratio	AHR*
<b>Stunting</b>	Y	91	13	13.0 (7.5-22.4)	1.9 (1.0-3.8)	-	31	31.0 (21.8-44.1)	1.1 (0.74-1.7)	-	4	3.7 (1.4-9.9)	1.8 (0.45-6.0)	-
	N	294	21	6.6 (4.3-10.1)	1	-	87	27.4 (22.2-33.8)	1	-	9	2.6 (1.4-5.0)	1	-
<b>Wasting</b>	Y	105	19	17.3 (11.1-27.2)	3.5 (1.8-6.8)	2.1 (1.0-4.5)	47	42.9 (32.2-57.1)	1.8 (1.3-2.7)	1.5 (1.0-2.3)	7	5.9 (2.8-12.4)	4.7 (1.4-16.2)	2.7 (0.7-10.6)
	N	280	15	4.9 (2.9-8.1)	1	-	71	23.0 (18.3-29.1)	1	-	6	1.8 (0.8-4.0)	1	-

\* Adjusted for factors significantly associated with the outcome in univariate analysis, AHR=adjusted hazard ratio

<sup>a</sup> data missing for n=3

## **6.4 Discussion**

### **6.4.1 Retention in care**

The study demonstrated that nurse-led HIV care for children and adolescents is feasible in primary care settings. The rate of retention in care was comparable to that reported in facility-based settings and higher than that reported in a recent retrospective cohort study of children attending decentralised care in Swaziland (184,187). Provision of HIV care in primary care facilities reduces the distance that patients need to travel to access treatment, and this may help improve retention in care (171,184). Notably, the rate of retention in care was significantly lower in those who did not start ART, with half of those who did not initiate ART being loss-to-follow up (LTFU). This finding has been reported previously and may be because patients perceive no benefit in attending for care if they are not receiving treatment (188,189). The 2015 WHO guidelines recommend initiation of ART regardless of disease stage or age and this may facilitate retention in care (117).

### **6.4.2 Virological suppression**

Worryingly, only two thirds of children achieved HIV virological suppression after starting ART, similar to the proportion reported in a recent study in a clinic in a central hospital in Harare (190). A systematic review of virological suppression rates of adolescents in both high and low- income settings countries demonstrated that 27-89% achieved virological suppression (191). The review reported on both cohort and cross sectional studies with various timepoints post ART start included. More recently Boerma et al described virological suppression rates among children and adolescents less than 18 years in low- and middle-income countries (192). In that meta-analysis, while reporting that virological suppression has improved since 2000, in the more recently analysed period of 2010 and beyond just under 63% of children and adolescents were virologically suppressed. This high rate of virological non-suppression amongst this age group is a concern. The risk of onward transmission as adolescents become adults and engage in relationships and have children will be high as will the possibility of transmitting drug resistant HIV infection.

There were no drug-stock outs over the duration of the study and so the virological non-suppression most likely reflects suboptimal adherence. Efforts to support adherence in this age group are urgently needed to improve virological suppression rates.

This highlights the urgent need for close monitoring of HIV viral load in this age-group. Since study completion, viral load testing has become available at primary care clinics within Zimbabwe's health service. Children are expected to take ART for at least two decades longer than adults and the need for interventions in this age-group to support sustained adherence to minimise emergence of drug resistance cannot be over-emphasized, particularly in resource-limited settings-where options for second and third line ART are limited.

### **6.4.3 Co-morbidities prompting unscheduled visits, hospitalisation and death**

Despite a good immunological response to treatment, a high frequency of PHC attendances occurred outside scheduled clinic appointments. Most unscheduled presentations were, however, due to minor illness and were managed at primary care level, with only a minority resulting in referral to hospital for further management. Such referrals were based on severity of the clinical presentation. Decentralised HIV care therefore provides a system for triage and reduces the burden on secondary health facilities, making it a sustainable system for long term care provision.

The leading cause of unscheduled visits, hospitalisation and death was respiratory tract infections, even among patients on ART. Of note, the majority of hospitalisations and death occurred amongst those on ART. This is explained by the those starting ART having a lower CD4 count or advanced WHO stage at time of ART initiation and therefore more susceptible to infection and advanced illness. However, it is not thought that any of the illnesses were related to immune reconstitution syndrome. Studies have reported a high burden of chronic lung disease in perinatally-infected children and adolescents, which is associated with considerable morbidity including recurrent respiratory tract

infections, poor lung function and reduced exercise tolerance (193). Indeed, there was a high prevalence of chronic respiratory symptoms at baseline evaluation (see chapter 3) as well as spirometric abnormalities. The recurrent respiratory tract infections observed in this study may be due to underlying chronic lung disease. The pathogenesis is poorly understood but is thought to be a sequela of chronic infections and/or HIV-mediated chronic inflammation. Once established chronic lung disease appears to be poorly responsive to ART, and children with recurrent respiratory tract infections may require further interventions such as additional prophylactic antibiotics or anti-inflammatory agents (194). Also notable is that pneumococcal vaccine was not part of the childhood vaccination programme in Zimbabwe when study participants were of an age for vaccination.

Notably, eight hospitalisations were TB-related, four of them resulting in death, despite systematic screening for TB following HIV diagnosis through sputum testing and at each follow up through WHO symptom screening. This demonstrates the low sensitivity of the WHO TB screening tool, and reflects the paucibacillary nature of TB in children. TB preventative therapy using isoniazid prophylaxis had not been widely implemented in Zimbabwe at commencement of the study and no participant received it over the study period. Screening for latent TB infection is not routinely performed. Skin disease was the second most common cause of unscheduled visits to PHCs. Recurrent skin infections are strongly associated with HIV infection in children, and in high HIV prevalence settings should prompt HIV testing (137,195). Side-effects of ART accounted for only 15% of unscheduled attendances. Importantly, most patients with side-effects were managed in primary care necessitating few drug switches, all effected at primary care level.

As has been reported in other studies, advanced disease stage and immunosuppression were risk factors for both hospitalisation and death (196,197). The median CD4 count at diagnosis was 375 cells/mm<sup>3</sup>, and the median age at diagnosis in a cohort where nearly all participants were infected perinatally was 11 years, implying an average delay of a decade in diagnosing HIV

infection. Given the high HIV-associated mortality observed in infants, there is limited awareness that a third of HIV-infected infants survive to adolescence even without treatment (4). Therefore, HIV testing is only offered when children present with conditions indicative of HIV infection, by which time they have often developed advanced disease (6). However, at least a quarter of children retained high CD4 counts ( $>500\text{cells/mm}^3$ ) and remained ineligible for ART based on current national guidelines. While a sub-group of these may be true long-term non-progressors or elite controllers, many remain pauci-symptomatic and may not prompt healthcare workers to offer HIV testing.

Older age was associated with more frequent unscheduled visits but not death and hospitalisation. This might reflect a combination of survival bias and longer life-time exposure of uncontrolled viraemia. While these children survived into older childhood without major illness, uncontrolled viraemia may have resulted in a higher prevalence and more prominent chronic disease phenotype such as chronic lung disease.

#### **6.4.4 Strengths and limitations of the study**

The strengths of the study were the prospective design and that participants were actively followed up to ascertain outcomes. Detailed clinical data were collected to establish the reasons for visits to health facilities and cause of death. The study was conducted in public sector services and therefore the findings are broadly generalisable. Although demonstrating high retention rates and low rates of loss-to-follow, it is possible that as participants were enrolled in study and receiving care from supervised and motivated nurses that such retention rates may not be fully reproducible in a generalised primary care setting in Zimbabwe.

Limitations include the lack of viral load data in all participants (73% of those eligible had viral load measured). There is a risk that the Cox proportional hazard models for death and admission may be over-fitted due to a small number of events. To mitigate this risk, no variables were specified a priori. Diagnoses such as respiratory tract infections were made in PHC were based on symptoms and

clinical examination, as diagnostic facilities are limited. Although treatment and care was provided by research nurses with a physician backup, national guidelines for treatment and management of children living with HIV were used. Staff within the primary health care clinics where our study was performed, who similar to the model used in the study, have physician support weekly.

The consultation fee of USD1 per child's visit could potentially be a barrier to children and adolescents ability to access care. In the case where a child was unable to afford the charge then the study paid the fee.

### ***6.5 Implications of study findings***

This study shows that decentralised nurse-led HIV care for children is possible and results in clinical outcomes comparable to those reported in children elsewhere in southern Africa (184). Implementation of 2015 WHO guidelines that recommend universal treatment of all HIV-infected individuals, is likely to result in a substantial increase in children eligible for treatment, particularly given the current low ART coverage (117). Considerable investment in age-appropriate HIV training and support for primary health care providers and interventions to support adherence need to be strengthened to achieve universal access and optimum treatment outcomes among children and adolescents.

## **7. Conclusions and Recommendations**

### **7.1 Key findings**

- 1) The majority of the children recruited into the cohort study were infected perinatally. This implies a long delay in HIV diagnosis and the study showed that many children had previously missed opportunities for HIV diagnosis. Although testing for infants and younger children have been strengthened through early infant diagnosis as part of PMTCT programmes, there are few systematic and age-appropriate approaches for HIV testing and counselling for older children. The first point of entry into the HIV care cascade is testing. If diagnosis is delayed then ART commencement will be delayed setting up a cycle of increased morbidity amongst this age group by the time ART is commenced. Delayed diagnosis of HIV infection in older children and adolescents in a setting of high HIV prevalence warrants urgent attention. Inclusion of younger age groups in testing initiatives is necessary to ensure ease of entry into the HIV care cascade. This finding also has implications for children of migrants accessing HIV care in resource rich settings such as Europe and U.S. The importance of index linked testing for all attendees at HIV clinics in such a setting is even more relevant, to ensure their children are screened for HIV infection. Which may have been acquired perinatally but not diagnosed in their country of birth.
- 2) This study has shown that there is a substantial degree of chronic morbidity at the time of HIV diagnosis. Not all of these conditions met CD4 or WHO staging criteria for ART commencement at the time of the study.
- 3) Fragile caregiving arrangements and silence within families about HIV was frequently reported. Disclosure was particularly low amongst the 6-10 year old age group.
- 4) After 18 months of ART, this cohort demonstrated a good immunological response, but the proportion who achieved viral suppression was low, likely due to poor adherence. Efforts to strengthen adherence in this age

group are needed and could include use of mobile technology, to enable health care providers send reminders at times medication is due, when to attend for review and also link peers to each other to support each other . However, in low-income settings “smart-phone” technology is not available to all but as costs of such technology decrease it is a future area for development.

- 5) Nurse led care was demonstrated to be feasible in this setting, with low rates of side effects and hospitalisation events recorded. Retention in care was high with low numbers of children being lost to follow up.

## ***7.2 Implications of Research Findings***

### **7.2.1 Chronic morbidity**

The high burden of chronic morbidity shown at time of diagnosis affected multiple physiological systems. Stunting of growth, delayed pubertal development as well as effects on respiratory tract were demonstrated. The exact pathogenesis for this is unknown however HIV is associated with chronic dysregulated systemic immune activation, that may also play a role in the maturation of a child’s immune system and so leave them susceptible to multiple chronic infections, that may not be reversible with ART (198). The SMART trial, performed in people over 13 years old, found high rates of non-infectious events, particularly cardiovascular, in those who had treatment interruption and decline in CD4 cells, which adds to the evidence of continuous immune activation in the background causing chronic systemic effects.

Since 2015, all children are ART eligible at time of diagnosis, regardless of age, their ART response will need to be charted and how this may or may not improve established chronic disease (117). ART has been shown to improve catch up growth in younger children and delay in ART initiation may affect catch up growth (82,83,199).

A recent study from Harare describing echo-cardiographic findings of older children established on ART living with perinatally acquired HIV, demonstrate that despite a high proportion of children being optimally controlled on ART, over one third had evidence of left heart abnormalities but without displaying overt symptomatology (200).

However, ART in itself will not be sufficient to deal with the chronic morbidities described. Interventions to address disability consequent to chronic clinical complications will be required. Dermatological conditions and chronic lung disease associated with chronic HIV infection have few if any therapies and can affect an adolescent's quality of life.

A limitation of this study is inability for this research group, to create a cohort for prospective surveillance of participants as they reach adulthood. However, it was outside the remit of funding.

### **7.2.2 Psychosocial morbidity**

Caregivers are uncertain how to talk about and when to discuss their children's HIV diagnosis with them. In particular, in this study we noted that caregivers felt that a potential lack of understanding of HIV infection on behalf of the child, was a reason to not talk about HIV. However, knowing one's HIV status has a positive impact on adherence and retention in care (150). It is vital that children are educated and supported in their life long condition so they can understand the consequences and implications of their illness. As children and adolescents mature they will need appropriate skills to manage their condition and take responsibility for management of their illness. Education of caregivers to empower them to discuss a complex condition in simpler, child friendly terms may prove beneficial (167).

Caregivers are aware of the need to disclose to the children in their care but are unsure of the how and the where (101). Caregiver factors may also be at play and their lives and social factors need to be taken into account so that a caregiver-child unit is aided as a whole and not just seen as each part been an individual (152). The

recent WHO guidelines recommend treatment of all individuals following HIV diagnosis regardless of age and disease stage (“Treat all”) yet the disclosure process for healthcare providers and caregivers remains a challenge and may hinder the process of ART scale up if wider societal issues regarding disclosure are not taken into account (201).

Ongoing communication with children and adolescents throughout their treatment to address questions about their clinical and social challenges are important to help support and inform them of the effect of HIV infection on their physiological makeup but also on how it may be impacting on their social inclusion. Children and adolescents living with HIV have reported a higher prevalence of mental health challenges and disability in comparison to their uninfected peers and also fall behind a grade or more in school and miss more days in the school year when compared to uninfected children from the same localities and within the same socio-economic status (200).

A better understanding of how grief and fluidity of caregivers may impact on children’s ability to cope and adhere to medications is needed. Addressing such potentially complex societal issues may help to bring about an improvement in clinical and virological outcomes if they are indeed a barrier to adherence. The silence surrounding HIV within families and difficulties surrounding onward disclosure to members of the community who may serve as potential supports for children living with HIV should be tackled to maximise a community’s role in helping children and adolescents live life openly.

### **7.2.3 HIV care outcomes**

This study presented findings of decentralised care and helps to inform programmes on how children and adolescents care is not compromised by decentralisation. Mentoring and training of healthcare staff is essential for successful implementation of decentralised care with task shifting to lower cadres of healthcare providers. This harbours well for test and treat initiative. Tackling the barriers to adherence remains a substantial barrier in this age-group. There is a scarcity of evidence for effective adherence interventions and

clearly a need for more research (202,203). Evidence is awaited on how differentiated care programmes that move away from “one size fits all approach” might bridge the gap to help engage children and adolescents more successfully in treatment (177).

### **7.3 Summary**

This subgroup of people living with HIV (PLHIV) represent a unique challenge to healthcare providers in both clinical and social aspects of care. Over the past two decades there has been an increase in migration from SSA to resource rich countries. It is important that health care providers in these setting are mindful when treating adults from countries of high HIV prevalence to ensure to adopt index linked testing of family members in the household- in particular UNAIDS has set ambitious 90-90-90 targets as defined by 90% of people living with HIV knowing their status, 90% of those aware of their status accessing treatment and 90% of those on treatment achieving virological suppression, all by 2020 (1). The findings of this work suggest that such targets for youth are not so easily attainable. Engagement of children, adolescents and their guardians at each stage of the HIV care cascade needs to be enhanced. Earlier diagnosis may prevent the chronic morbidity described in this work. Further understanding on how social background and guardianship impacts on children’s care outcomes and interventions to improve rates of virological outcomes needs to be developed.

The definition of health according to WHO encompasses more than just the physical state, it also takes into account the mental and social well-being of the person (204). With ART now becoming within most populations reach, it is time for the focus to shift to expand our vision to a healthier future for our younger generation living with HIV and to expand the focus of health according to WHO definition.

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## Appendix A. Drug Dosing in Children

### A1.1 NRI Dosing in Children

Weight Range (Kg)	Drug combination	No Of Tablets	
		AM	PM
14-19.9 kg	<b>AZT+ 3TC (FDC12)</b> (AZT=120mg + 3TC=60mg)	1.5	1
20-24.9kg	<b>AZT + 3TC (FDC 12)</b> (AZT=120mg +3TC=60mg)	1.5	1.5
25kg and over	<b>AZT + 3TC (FDC 30)</b> (AZT=300mg +3TC=150mg)	1	1
14-19.9 kg	<b>D4T + 3TC</b> (d4T=12mg + 3TC=60mg)	1.5	1
20-24.9kg	<b>D4T + 3TC</b> (d4T= 12mg +3TC=60mg)	1.5	1.5
25kg and over	<b>D4T + 3TC (Adult)</b> (d4T= 30mg +3TC=150mg)	1	1
>12 years	<b>TNF+3TC (Tenolam)</b> (TNF=300mg +3TC= 300mg)	1	-

Triomune Junior: (d4T=12mg + 3TC=60mg + NVP=100mg)

If only Triomune Baby available- use double the number of tablets as Triomune Junior

### A1.2 NNRTI Dosing in Children

#### A1.2.1 Nevirapine

Weight Range (Kg)	NO. of TABLETS (1tablet=200mg)			
	First two weeks (initiation phase)		After two weeks (maintenance phase)	
	AM	PM	AM	PM
14-19.9 kg	-	1	½	1
20-24.9kg	-	1	½	1
25kg and over	-	1	1	1

**A1.2.2 Efavirenz (>3years only)**

<b>Weight Range (Kg)</b>	<b>PM</b>	<b>No of Tablets</b>	<b>Total Dose</b>
14-19.9 kg	5*(50mg)	5	250mg
20-24.9kg	1/2*(600mg)	0.5	300mg
25-29.9kg	1/2*(600) + 1*(50mg)	1.5	350mg
30-34.5kg	1/2*(600) + 2*(50mg)	2.5	400mg
>35kg	1*(600mg)	1	600mg

**A1.2.3 Lopinavir/Ritonavir Dosing in Children**

<b>Weight Range (Kg)</b>	<b>NO OF TABLETS</b>	
	<b>AM</b>	<b>PM</b>
<b>USE PAEDIATRIC TABLET (100/25)</b>		
14-19.9 kg	2	2
20-24.9kg	3	2
<b>USE ADULT TABLET (200/50)</b>		
25-34.9kg	2	1
35 kg and over	2	2

**Appendix B. Tanner Staging**

<b>Tanner Stage</b>	<b>Breasts (female)</b>	<b>Pubic Hair (male and female)</b>	<b>Male Genitals</b>
<b>I</b>	No glandular tissue: areola follows the skin contours of the chest [Age ≤10]	No (coarse, pigmented) pubic hair at all [Age ≤10]	Testicular volume less than 1.5 ml; small penis of 3 cm or less) [Age ≤9years]
<b>II</b>	Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen [Age 10-11.5]	Small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females) [Age 10–11.5]	Testicular volume between 1.6 and 6 ml; skin on scrotum thins, reddens and enlarges; penis length unchanged [Age 9-11]
<b>III</b>	Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast [Age 11.5-13]	Hair becomes more coarse and curly, and begins to extend laterally [Age 11.5–13]	Testicular volume between 6 and 12 ml; scrotum enlarges further; penis begins to lengthen to about 6 cm [Age 11-12.5]
<b>IV</b>	Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast [Age 13-15]	Adult-like hair quality, extending across pubis but sparing medial thighs [Age 13–15]	Testicular volume between 12 and 20 ml; scrotum enlarges further and darkens; penis increases in length to 10 cm and circumference [Age 12.5-14]
<b>V</b>	Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla. [Age 15+]	Hair extends to medial surface of the thighs [Age 15+]	Testicular volume greater than 20 ml; adult scrotum and penis of 15 cm in length [Age 14+]

**Appendix C. Journal Article: McHugh G *et al.* Journal of Acquired Immune deficiency Syndrome, Volume 73, Issue 3, Nov 2016**

**Chronic morbidity among older children and adolescents at diagnosis of HIV infection.** Grace McHugh, Jamie Rylance, Hilda Mujuru, Kusum Nathoo, Prosper Chonzi, Ethel Dauya, Tsitsi Bandason, Victoria Simms, Katharina Kranzer, Rashida A Ferrand. *J Acquir Immune Defic Syndr* 2016; 73:275–281

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## **Chronic morbidity among older children and adolescents at diagnosis of HIV infection**

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## **Abstract**

### ***Background***

Substantial numbers of children with HIV present to health care services in older childhood and adolescence, previously undiagnosed. These “slow-progressors” may experience considerable chronic ill-health, which is not well-characterised. We investigated the prevalence of chronic morbidity among children aged 6-15 years at diagnosis of HIV infection.

### ***Methods***

A cross sectional study was performed at seven primary care clinics in Harare, Zimbabwe. Children aged 6-15 years who tested HIV positive following provider-initiated HIV testing and counselling were recruited. A detailed clinical history and standardised clinical examination was undertaken. The association between chronic disease and CD4 count was investigated using multivariate logistic regression.

### ***Results***

Of the 385 participants recruited (52% female, median age 11 years (IQR 8-13)), 95% were perinatally HIV-infected. The median CD4 count was 375 (IQR 215-599) cells/mm<sup>3</sup>. Although 78% had previous contact with health care services, HIV testing had not been performed. There was a high burden of chronic morbidity: 23% were stunted, 21% had pubertal delay, 25% had chronic skin disease, 54% had a chronic cough of more than 1 month’s duration, 28% had abnormal lung function and 12% reported hearing impairment. There was no association between CD4 count of <500cells/mm<sup>3</sup> or <350 cells/mm<sup>3</sup> with WHO stage or these chronic conditions.

### ***Conclusion***

In children with slow-progressing HIV, there is a substantial burden of chronic morbidity even when CD4 count is relatively preserved. Timely HIV testing and prompt ART initiation are urgently needed to prevent development of chronic complications.

## Background

Untreated vertically-acquired HIV infection is associated with high mortality rates with a 50% probability of dying by two years of age among African cohorts in the pre-antiretroviral therapy (ART) era.(4) However, as HIV epidemics have matured, survival estimates have been successively revised upwards and a substantial number of perinatally-infected children are presenting with HIV infection in later childhood or adolescence. (75,79,114) It is estimated that a third of HIV-infected infants have slow-progressing disease with a median survival of at least 16 years.(76) Unlike children who have rapid disease progression and present with AIDS-defining illness in infancy, children with slow progressing HIV are either pauci-symptomatic or typically have a history of multiple, non-specific complaints, including recurrent upper respiratory-tract or skin infections that are also common among their HIV-uninfected peers. (5,115). Recognition of HIV is consequently often delayed until presentation with advanced disease. (5)

There is strong evidence that immediate initiation of ART reduces mortality in infants , in particular those under 1 year of age.(4) The WHO 2013 HIV treatment guidelines recommend immediate ART initiation on diagnosis regardless of clinical or immune stage in all children aged under five years.(9) Such a benefit has not been demonstrated for older children.(116) For those over five years, WHO 2013 guidelines (which were standard of care when this study was being conducted) recommended that, as for adults, ART is deferred until the clinical Stage 3 or 4 HIV disease is apparent or if the CD4 count drops below 500 cell/mm.(9) In 2015 the WHO further revised HIV treatment guidelines recommending that ART be commenced in all age groups regardless of clinical or immune status, although evidence for immediate ART commencement is lacking in older children and adolescents.(117)

While the risk of AIDS-defining infections is low above a CD4 threshold of 500 cells/mm<sup>3</sup>, longstanding infection is associated with development of chronic complications, which may not fulfil the criteria for ART initiation.(118) For example, we have previously demonstrated a high prevalence of chronic

respiratory symptoms among adolescents with vertically-acquired HIV infection. However, objective measures of lung function were not performed and the study included both ART-naïve and ART-treated individuals.(87)

We investigated the prevalence of chronic symptoms, including a standardised assessment of growth and lung function and whether these were associated with immunological status among children aged 6-15 years at HIV diagnosis of HIV infection.

## **Methods**

### ***Study setting***

A cross sectional study was carried out in seven public sector primary healthcare clinics (PHCs) in seven high population density suburbs in southwest Harare, Zimbabwe between January 2013 and December 2014. Each suburb in Harare is served by one main PHC, termed polyclinic, which provides acute primary care, antenatal and postnatal care, mother and child health services, HIV testing and care. Primary health care provision is nurse-led, supported by weekly consultation visits by a general medical practitioner. Children are managed using WHO Integrated Management of Childhood Illness (IMCI) protocols with referral to the local hospital where required.(119)

ART and cotrimoxazole prophylaxis are provided free of charge, although each HIV consultation visit incurs a cost of US\$1. Provider-initiated HIV testing and counselling (PITC) i.e. offering HIV testing to all individuals attending health facilities regardless of the reason for presentation has been part of WHO and Zimbabwean national guidelines since 2007 and testing is free of charge.(205,206) Nurse-led ART initiation for children was introduced at the seven PHCs with supervision from a physician (clinics having previously only provided ART for those having been initiated on treatment in secondary healthcare facilities). Nurses were trained on HIV counselling and management, and ART was provided according to national guidelines. Until February 2014, participants were initiated on ART if their CD4 was below 350 cells/mm<sup>3</sup> or had

WHO Stage 3 or 4 infection. From March 2014, Zimbabwe adopted the WHO 2013 consolidated guidelines, with the threshold for ART initiation revised to 500 cells/mm.<sup>(9)</sup> All children were commenced on cotrimoxazole prophylaxis at diagnosis of HIV infection.

Children aged between 6 and 15 years who tested HIV-positive at the study PHCs were offered enrolment into the study. Children were excluded from the study if they resided outside of Harare, as follow up may have been difficult due to distance to travel to attend clinical review.

### ***Clinical Assessment***

Clinical history was recorded using an interviewer-administered questionnaire. Contact with health services, history of past illness, exposure to ART including maternal ART for prevention of mother-to-child HIV transmission (PMTCT), drug history, and acute and chronic symptoms were recorded, including respiratory and gastrointestinal symptoms, and problems with hearing, vision, speech and gross motor function. HIV infection was staged using the WHO Staging System and a CD4 count.<sup>(120)</sup>

A standardized physical examination was carried out, including inspection of the skin for herpes zoster scarring, papular pruritic eruptions, planar warts, verrucous warts, molluscum contagiosum, fungal infection and Kaposi sarcoma. The oral cavity was examined for gingivitis, periodontitis, candidiasis and Kaposi sarcoma. Anthropometric examination included measurement of height and weight. The head circumference was determined by measuring the greatest occipito-frontal circumference, with the larger of two readings recorded. Tanner pubertal staging was performed in children aged > 9 years.<sup>(123)</sup> In females, breast and pubic hair development and age at menarche were recorded. In males, testicular volume, measured using an orchidometer, pubic hair development and penile length were assessed.

Cardiorespiratory function was assessed by the MRC Dyspnoea Scale Score and modified incremental shuttle walk test (ISWT) with pre- and post- test recording of respiratory rate, heart rate and peripheral oxygen saturations.(124,125) ISWT was not performed if baseline oxygen saturation was less than 88%, or if resting heart rate or respiratory rate exceeded 120 and 30 per minute respectively. Spirometry was performed by trained nurses using an EasyOne™ World spirometer (NDD Medical Technologies, Inc., Andover, MA, USA). After demonstration of the procedure, the participant performed forced exhalation manoeuvres while seated until quality criteria had been reached or 8 trials had been completed. The trial with the highest forced expiratory volume at one second (FEV1) and forced vital capacity (FVC) were selected for interpretation. Reversibility testing by repeat spirometry was performed 15 minutes after administration of 2.5mg of nebulised salbutamol, if any abnormality i.e. either obstruction as defined by FEV1: FVC of less than 1.64 SD below the mean or restriction as defined by FVC <1.64SD below mean with normal FEV1:FVC ratio, was present.(126)

### ***Laboratory Investigations***

CD4 count was measured using an Alere PIMA™ CD4 machine. Full blood count, renal and liver function tests are not a prerequisite for starting ART in national guidelines and these were only performed if clinically indicated. Participants who screened positive on the WHO TB screen were asked for a sputum sample.(121) Sputum was examined onsite by Ziehl-Nielsen smear microscopy and Xpert TB™.

### ***Data management and analysis***

Data was collected from paper forms by optical mark recognition (Cardiff TELEFORM Intelligent Character, Version 10.7) and analysed using STATA, version 12.1 (STATA Corporation, USA). Z-scores for height-for-age, weight-for-age and head circumference-for-age were calculated using the 1990 British growth reference curves.(129) Spirometric indices were expressed as z-scores using GLI2012 reference ranges.(128) The association between a priori defined

variables and CD4 count was determined using logistic regression, adjusting for age and sex. Missing variables were excluded in logistic regression analysis.

### ***Clinical definitions***

A z-score of  $<-2$  for height-for-age and weight-for-age were considered to represent stunting and wasting respectively. Pubertal delay was defined as girls not having reached Tanner 2 breast development by age 12 years and boys not having reached Tanner 2 testicular volume by age 14 years. (127) An obstructive lung defect was defined as FEV1 less than 1.64 standard deviations (SD) below the mean and FEV1: FVC of less than 1.64SD below the mean. A reduced FVC (which would be suggestive of restrictive defect) was defined as an FVC below 1.64SD below the mean with a normal or increased FEV1: FVC ratio.(128) Reversibility of either obstructive or restrictive defect was defined as greater than or equal to 12% improvement in FEV1 after repeat spirometric testing post administration of salbutamol.(126)

### ***Ethical Considerations***

Written informed consent was obtained from all caregivers and written assent obtained from participants. Ethical approval for the study was obtained from the Medical Research Council of Zimbabwe, the Harare City Health Department Ethics Committee, the Biomedical Research and Training Institute Institutional Review Board and the London School of Hygiene and Tropical Medicine Ethics Committee.

### **Results**

During the study period 9,655 children were tested for HIV of whom 449 (4.6%) tested HIV-positive. An additional 21 participants were identified who had been diagnosed prior to study commencement but had not engaged in care and/or had not commenced ART. In total 385 (86%) participants were recruited into the study. The remainder were not enrolled due to residence outside the study area (n=24, 5%), declined consent (n=25, 5.5%), care sought elsewhere (n=34, 7.5%) and wrong age (n=2, 0.4%). The median age at diagnosis was 11 years (IQR 8-

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13) and 52% were female. The majority of participants were infected through mother-to-child transmission based on a history of maternal or natural sibling HIV or death, and self-report of no sexual debut, blood transfusions or surgery and less than 2% of mothers of participants had received ART for PMTCT. Although 78% of participants had attended a PHC in the past 6 months and/or been previously hospitalized, HIV testing had not been performed (Table 1).

More than half of participants rated their health in the past 3 months as poor (Table 2). Chronic respiratory symptoms were frequent with 54% reporting cough of more than one month's duration and 16% reporting dyspnea. At rest, 12% had oxygen saturations <88% and a further 10% dropped their oxygen saturations below 88% following exercise. Of the 238 participants who underwent spirometry and were able to produce quality traces, 23 (10%) had obstructive lung function defect with only three demonstrating reversibility with salbutamol, and 43 (18%) had a reduced FVC. Notably, despite 155 (40%) screening positive for TB on the WHO screen, only one participant was found to have TB on GeneXpert.

The median height-for-age, weight-for-age and head circumference-for-age z-scores were -1.2 (IQR -1.9 to -0.41), -1.1 (IQR -2.1 to -0.45) and -1.4 (IQR -2.4 to -0.66) respectively. In addition, 27% of girls and 13% of boys were considered to have pubertal delay and 24% of girls aged 15 years had not experienced menarche. Of the 80 participants with WHO stage 4 disease, 66% were classified as such based on stunting alone. Other chronic impairments included hearing difficulties self-reported by 12%, visual impairment by 6% and speech impairment or gross motor defects by 2%. Chronic skin disease was found in 25% of participants on examination.

The median CD4 count was 375 cells/mm<sup>3</sup> (IQR 215-599) and 40% had WHO Stage 3 or 4 HIV infection. Using a CD4 count threshold of 350 cells/mm<sup>3</sup> and/or WHO stage 3/4 disease, 67% children were eligible for ART, this figure increasing to 78% if the threshold was changed to 500 cells/mm<sup>3</sup>. Using logistic regression analysis adjusted for age and sex, participant self-report of ill-health in the past

three months was associated with a CD4 count  $<350$  cells/mm<sup>3</sup> (aOR 1.89 95% C.I 1.25-2.88) as was having a chronic skin condition (aOR 1.65 95% C.I 1.02-2.69). However, a CD4 count  $<350$  cells/mm<sup>3</sup> or  $<500$  cells/mm<sup>3</sup> was not associated with WHO stage, reduced FEV<sub>1</sub> or FVC z score or growth parameters such as height-for-age, weight-for-age or head circumference z-scores (Table 3).

## Discussion

The main finding of this study was the heavy burden of chronic morbidity among older children and adolescents at time of HIV diagnosis. Consistent with other studies, a quarter of participants had stunting and 23% had pubertal delay.(84,85,130) Although catch-up growth can be achieved after initiation of ART, children who begin treatment in later childhood are typically unable to regain their height potential.(82,131) In addition, more than a third of participants had a head circumference-for-age z-score less than -2, which could partly be explained by sub-optimal brain growth in early childhood. Unlike the progressive encephalopathy, manifest as failure to attain or loss of developmental milestones or intellectual capacity and motor defects, that is typical in HIV-infected infants and young children, gross motor defects and speech impairment was rare among our participants with slow-progressive disease. However, studies have reported defects in seemingly asymptomatic HIV-infected children in fine motor function, memory, perceptual performance, quantitative abilities, and mental processing and language abilities.(132,133) These deficits are subtle and are not easily identified on routine questionnaire and therefore without formative testing may have been an underrepresentation of degree of morbidity in relation to higher functioning capacity in our study. These findings have to be interpreted with caution, however, as Western references ranges for head circumference were used due to a lack of normative data from African children, and head circumference does vary by ethnic group.(129)

Chronic respiratory disease was common with cough, hypoxia, reduced exercise tolerance and obstructive lung defects being the predominant features.

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Reversibility was rare, making asthma unlikely. Other studies have also shown a high prevalence of obstructive lung defects, with little or no reversibility. (207):(134) A study which performed chest computed tomography in adolescents with longstanding, vertically-acquired HIV infection showed that constrictive obliterative bronchiolitis (OB) was the predominant cause of chronic lung disease, with lymphoid interstitial pneumonitis (the most commonly recognised cause of lung disease in HIV-infected children) being a rare finding.(87,88,135) OB is a progressive, life-threatening condition and is well-recognised as sequelae of respiratory tract infections, which were commonly reported by participants.(136)

A quarter of all participants had chronic dermatological conditions. While not life-threatening, these are commonly recognised as stigmata of HIV infection, may take long periods to resolve following ART and for some conditions particularly planar warts, effective treatments are not available.(137,138)

Importantly, we observed no association between CD4 count and WHO HIV disease stage, a finding also noted previously.(139) There was also no association between CD4 count and chronic conditions, including stunting, and poor lung function. Taken together, this implies that CD4 count may not be an appropriate criterion for starting ART in older children. This also has potential implications with respect to timing of ART initiation. Based on the WHO 2013 HIV treatment guidelines, 12% of participants would not have been eligible for ART. Given the lack of evidence of the mortality benefit of immediate ART in older children and the concern about drug toxicity and adherence, guidelines until recently have recommended deferring ART in older children.(9) Recent trials in adults have demonstrated that early initiation of ART reduces the risk of AIDS and non-AIDS events,(90,140) but these trials excluded older children and adolescents. Our findings demonstrate that children with slow-progressing disease may have preserved CD4 counts but do develop chronic complications such as poor growth and chronic lung disease. It is thus possible that immediate ART may also prevent development of chronic complications in children. A randomised controlled trial would definitively establish whether immediate ART would prevent

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development or progression of chronic complications but this is not going to be possible given the recent change in WHO guidelines recommending immediate ART in all adults and children.

The scale-up of programs to prevent mother-to-child-HIV transmission (PMTCT) has resulted in a substantial decline in the numbers of children infected with HIV, but coverage remains sub-optimal in many high burden countries.(141) The limited availability of HIV testing services for children and the low rates of early infant diagnosis mean that for many infected infants, HIV diagnosis occurs in late childhood or adolescence following many years of ill health.(142) In this study, 78% of participants had previous contact with health facilities, including 27% having been hospitalised, but had not had HIV testing. Despite recommendations that PITC should be offered as standard in health facilities in HIV high prevalence settings, in practice, HIV testing is often prompted only after presentation with typical HIV-related symptoms.(143) Children with slow progressing disease may take years before they develop the well-recognised HIV indicator conditions that prompt an offer of HIV testing, by which time they develop chronic complications and organ damage which may not be reversible with ART once established.

To our knowledge this is the first study to report the prevalence of morbidity at HIV diagnosis in children and adolescents with longstanding HIV infection. The vast majority of children were vertically-infected, implying living with HIV infection for up to 15 years without prior treatment. Participants were diagnosed after optimised PITC of attendees regardless of cause of presentation, with 80% of all attendees with previously unknown HIV status undergoing HIV testing (data not shown). The study was based in primary care facilities and therefore was not biased towards sicker children. We acknowledge several limitations. There was no HIV-uninfected or an HIV-treated comparison group in our study. Vision, hearing, neurocognitive and musculoskeletal function were not formally assessed but relied on self-report. Lung function assessment was not carried out in 5% of participants. This was partly due to logistic reasons as respiratory assessment could not be performed at the initial assessment necessitating a second appointment within two weeks which some participants did not attend.

Spirometric traces could not be interpreted in 100 (26%) participants. In addition 19 (5%) participants were too ill to perform both spirometry and/or ISWT, which may have led to an underestimation of degree of lung disease present amongst the participants. Local reference ranges for lung function, puberty and head circumference are not available. British reference ranges were used for height and weight z-score calculations due to a lack of WHO weight-for-age reference ranges for children over 9 years of age, which may not be appropriate for an African population.

Our study shows a substantial burden of chronic morbidity among HIV-infected children diagnosed in later childhood, even among those with preserved CD4 counts. Recognition of this burden is needed to stimulate earlier diagnosis and improve access to HIV care for this age group. There is a pressing need to strengthen PITC and potentially provide other more effective services for HIV testing in this age group, and for timely institution of ART. Current recommendations of deferred ART in children may put them at risk of developing chronic complications. The recent WHO guidelines recommending treatment of all HIV-infected individuals regardless of age and disease stage, may reduce the risk of development of chronic complications. Studies investigating the impact of immediate ART on AIDS and non-AIDS events in children and the pathogenesis of chronic complications will inform development of optimum care provision for HIV-infected children.

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**Table 1: Baseline characteristics of participants at HIV diagnosis (N=385)**

<b>Characteristic</b>	<b>N (%)</b>
<b>Demographic</b>	
Median (IQR) age, years	11 (8-13)
Female	199 (52%)
<b>Clinical history</b>	
Previous hospitalisation	105 (27%)
Attendance at PHC in past 6 months	268 (70%)
Previous TB treatment	18 (5%)
Recurrent upper respiratory tract infection	107 (28%)
Previous herpes zoster infection	41 (11%)
<b>HIV History</b>	
Mother or child received ART for PMTCT	5 (1%)
Circumstances leading to HIV test	
Attended PHC due to symptoms, first HIV test	323 (84%)
Previously tested but unengaged in care	19 (5%)
Attended PHC for HIV testing	43 (11%)
Likely HIV mode of acquisition	
Mother-to-child transmission	366 (95%)
Parenteral	6 (2%)
Horizontal	12 (3%)
Unknown	1 (0%)
Median (IQR) CD4, cells/mm <sup>3a</sup>	375 (215-599)
CD4 count at diagnosis, cells/mm <sup>3</sup>	
<200	88 (23%)
200-499	162 (42%)
≥500	132 (35%)
WHO Stage	
1/2	229 (59%)
3/4	156 (41%)

<sup>a</sup>Data missing for 3 participants

**Table 2: Chronic morbidity in study participants**

<b>Characteristic</b>	<b>n (%) of participants</b>
Self-rated general health fair or poor in past 3 months <sup>a</sup>	197 (52%)
Fevers in the past month	162 (42%)
Diarrhoea	130 (34%)
Loss of appetite	92 (24%)
Oral candidiasis	43 (11%)
<b>Growth and Sexual development</b>	
Height-for-age z-score < -2	91 (23%)
Weight-for-age z-score < -2	106 (27%)
Head circumference-for-age z-score < -2 <sup>b</sup>	134 (35%)
Body mass index-for-age z-score < -2	62 (16%)
Delayed puberty <sup>c</sup>	18 (21%)
Non occurrence of menarche by 15 years of age (n=17) <sup>d</sup>	4 (24%)
<b>Chronic Respiratory Disease</b>	
Chronic cough >1 month	206 (54%)
MRC Dyspnoea score $\geq 2$ <sup>e</sup>	46 (16%)
Digital clubbing	2 (0.5%)
SpO <sub>2</sub> <88% <sup>f</sup>	45 (14%)
Respiratory rate >30/min at rest <sup>g</sup>	14 (4%)
$\geq 5\%$ desaturation on exercise (n=246)	24 (10%)
FEV <sub>1</sub> z-score, mean, sd <sup>h</sup> (n=238)	-0.73 (1.41)
FVC z-score, mean, sd <sup>h</sup> (n=238)	-0.63 (1.35)
FEF 25%-75% z-score, mean, sd <sup>h</sup> (n=238)	-0.19 (1.13)
<b>Chronic skin disease</b>	
Any chronic skin condition	96 (25%)
Molluscum contagiosum	37 (10%)
Papular pruritic eruption	33 (9%)
Planar warts	31 (8%)
Verrucous warts	16 (4%)
<b>Other chronic conditions</b>	
Gingivitis/periodontitis	11 (3%)
Visual impairment	22 (6%)
Hearing impairment	46 (12%)
Gross motor defects	2 (0.5%)
Speech impairment	4 (1%)

<sup>a</sup>Data missing for 3 participants

<sup>b</sup>Data missing for 6 participants

<sup>c</sup>Defined as females not reaching Tanner breast stage 2 by 13 years, males not reaching Tanner testicular stage 2 by 14 years (denominator=87)

<sup>d</sup>17 females in this age group

<sup>e</sup>Data missing for 94 participants- 60 reason unknown, 18 missed resp assessment, 14 too ill, 1 mental impairment, 1 refused

<sup>f</sup>Data missing for 58 participants-18 reason unknown, 17 too ill, 16 missed appointment, 5 equipment malfunction, 1 mental impairment, 1 refused

<sup>g</sup>Data missing for 60 participants-20 reason unknown, 17 too ill, 16 missed appointment, 5 equipment malfunction, 1 mental impairment, 1 refused

<sup>h</sup>Data missing for 147 participants- 91 uninterpretable trace, 9 missing data, 19 too ill, 11 missed appointment, 9 did not grasp technique, 8 reason unknown

**Table 3: Association of clinical conditions with CD4 count at study enrolment**

	CD4 count <350 cells/mm <sup>3a</sup> (N=177)	CD4 count <350 cells/mm <sup>3</sup> aOR <sup>e</sup> (95% CI)	CD4 count <500 cells/mm <sup>3</sup> (N=250)	CD4 count <500 cells/mm <sup>3</sup> aOR(95% CI)
WHO stage 3/4	77 (44%)	1.25 (0.82-1.91)	107 (43%)	1.33 (0.84- 2.10)
Self-rated general health fair /poor in past 3 months <sup>b</sup>	106 (60%)	1.89 (1.25-2.88)	137 (55%)	1.49 (0.95-2.32)
Chronic skin condition	55 (31%)	1.65 (1.02-2.69)	72 (29%)	1.61 (0.93-2.79)
Height-for-age z-score <-2	43 (24%)	0.90 (0.55-1.48)	65 (26%)	1.27 (0.73-2.19)
Weight-for-age z-score <-2	56 (32%)	1.24 (0.77-1.99)	78 (31%)	1.50 (0.88-2.56)
Head circumference- for-age z-score <-2 <sup>c</sup>	57 (32%)	0.98 (0.63-1.54)	83 (33%)	1.12 (0.70-1.82)
Pubertal delay	9 (5%)	0.68 (0.25- 1.84)	15 (6%)	1.75 (0.47- 6.50)
Visual impairment	12 (7%)	1.32 (0.54-3.23)	18 (7%)	2.43 (0.77-7.66)
Hearing impairment	25 (14%)	1.41 (0.75- 2.66)	33 (13%)	1.29 (0.64-2.61)
FEV <sub>1</sub> z-score <-1.64 <sup>d</sup>	32 (18%)	1.39 (0.76-2.54)	42 (17%)	1.55 (0.78-3.09)
FVC z-score <-1.64 <sup>d</sup>	25 (14%)	1.41 (0.72 -2.76)	30 (12%)	1.09 (0.52-2.28)

<sup>a</sup>Data missing for 3 participants- laboratory error

<sup>b</sup>Data missing for 3 participants

<sup>c</sup>Data missing for 6 participants

<sup>d</sup>Data missing for 147 participants- 91 uninterpretable trace, 9 missing data, 19 too ill to perform Spirometry, 11 missed resp assessment, 9 did not grasp technique, 8 reason unknown

<sup>e</sup>Adjusted Odds ratio for age and sex

**Appendix D. Journal Article: McHugh G *et al.* Journal of the International AIDS Society 2017, 20:21843**

**Clinical outcomes in children and adolescents initiating antiretroviral therapy in decentralized healthcare settings in Zimbabwe.** McHugh G, Simms V, Dauya E, Bandason T, Chonzi P, Metaxa D, Munyati S, Nathoo K, Mujuru H, Kranzer K, Ferrand RA. Journal of the International AIDS Society 2017, 20:21843

Research article

# Clinical outcomes in children and adolescents initiating antiretroviral therapy in decentralized healthcare settings in Zimbabwe

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## Abstract

**Introduction:** Decentralized HIV care for adults does not appear to compromise clinical outcomes. HIV care for children poses additional clinical and social complexities. We conducted a prospective cohort study to investigate clinical outcomes in children aged 6–15 years who registered for HIV care at seven primary healthcare clinics (PHCs) in Harare, Zimbabwe.

**Methods:** Participants were recruited between January 2013 and December 2014 and followed for 18 months. Rates of and reasons for mortality, hospitalization and unscheduled PHC attendances were ascertained. Cox proportional modelling was used to determine the hazard of death, unscheduled attendances and hospitalization.

**Results:** We recruited 385 participants, median age 11 years (IQR: 9–13) and 52% were female. The median CD4 count was 375 cells/mm<sup>3</sup> (IQR: 215–599) and 77% commenced ART over the study period, with 64% of those who had viral load measured achieving an HIV viral load <400 copies/ml. At 18 months, 4% of those who started ART vs. 24% of those who remained ART-naïve were lost-to-follow-up ( $p < 0.001$ ). Hospitalization and mortality rates were low (8.14/100 person-years (pyrs) and 2.86/100 pyrs, respectively). There was a high rate of unscheduled PHC attendances (34.94/100 pyrs), but only 7% resulted in hospitalization. Respiratory disease was the major cause of hospitalization, unscheduled attendances and death. CD4 count <350 cells/mm<sup>3</sup> was a risk factor for hospitalization (aHR 3.6 (95%CI 1.6–8.2)).

**Conclusions:** Despite only 64% of participants achieving virological suppression, clinical outcomes were good and high rates of retention in care were observed. This demonstrates that in an era moving towards differentiated care in addition to implementation of universal treatment, decentralized HIV care for children is achievable. Interventions to improve adherence in this age-group are urgently needed.

**keywords:** HIV; Africa; children; retention in care; outcomes

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## Introduction

By 2015, an estimated 1.8 million children under 15 years of age were living with HIV globally, the majority in Sub-Saharan Africa, yet just half were accessing antiretroviral therapy (ART) [1]. While the number accessing HIV treatment represents gains from 2010, children lag disproportionately behind adults in terms of ART coverage (49% of all children infected were accessing ART in 2015 as compared to just 21% in 2010) [1].

As ART programmes have scaled up, the major barriers to ART access have been the lack of healthcare professionals to provide HIV care, overcrowding of clinics and distance to facilities where such care is available [2–6]. Among adults, the increase in numbers of individuals accessing ART has led to decentralization of HIV care provision from secondary to primary health care facilities, and task-sharing to involve nurses in treatment of HIV infection [7,8]. The aims of decentralization and task-sharing was to improve

access to care for patients and relieve pressure on heavily overburdened secondary care facilities [9]. More recently, differentiated care initiatives are focusing on providing services which are more client focused and tailored to specific needs of diverse populations of people living with HIV [10]. Zimbabwe has incorporated the concept of differentiated care into its recent HIV treatment framework [11].

Clinical outcomes among adults HIV care in decentralized programmes with nurse-led care have been comparable to those in secondary healthcare facilities [7,8,12,13]. Provision of HIV care to children and adolescents is associated with additional complexities, which may impact on clinical outcomes [9]. These include reliance on guardians, who are often not biological parents, for access to and retention in care, weight-based ART dosing, difficulties in discussing HIV and disclosing HIV status to children [14–16]. Older children and adolescents with HIV have higher rates of virological failure and attrition than adults [17,18]. These have led to a

relative reluctance by primary care level providers to provide HIV care to this age-group [19]. WHO guidelines now recommend “treat all” living with HIV and Zimbabwe, since 2016, has adapted its national guidelines to reflect this. Limited data are available on ART care provision to children by nurses in primary health care facilities [20]. We present clinical outcomes among children and adolescents accessing decentralized HIV care services provided by nurses in Harare, Zimbabwe.

## Methods

### Study setting

A prospective cohort study of children aged 6–15 years was conducted in seven primary healthcare clinics (PHCs) in south west Harare, Zimbabwe between January 2013 and December 2014. Opt-out HIV testing and decentralized, nurse-led HIV care for children was introduced at the seven PHCs with supervision from by a physician. Children found to be HIV positive were offered enrolment into the cohort which was then followed over 18 months’ duration. Clinics where the study was performed were treating adults with HIV infection on a nurse-led basis as per Zimbabwe national guidelines but had not been treating children living with HIV. Children were followed up by research nurses for 18 months from time of study enrolment. On completion of study follow up, HIV care and management was transferred to clinic nursing staff. Nurses in the employ of the clinic were trained on HIV care and management for children over the duration of the study. Although treatment and care was provided by research nurses with a physician backup, national guidelines for treatment and management of children living with HIV were used. Staff within the primary health care clinics where our study was performed, who similar to the model used in the study, have physician support weekly and were trained on management of paediatric HIV treatment in tandem with research nurses. Details of the study which includes baseline clinical data at time of enrolment have been described elsewhere [21]. Research nurses based at each clinic were trained on paediatric HIV testing and counselling and provision of HIV care, treatment monitoring and management of infections, based on the Integrated Management of Childhood Illness (IMCI) algorithm, over a 2-week period prior to study commencement [22]. The Ministry of Health and Child Care training tools were utilized and simple ART-dosing charts (available on request) were produced to facilitate weight-based dosing. Criteria for referral to secondary level facilities were pre-defined, including “danger signs” based on the IMCI algorithm. Nurses carried out ART eligibility screening, initiated ART and provided follow-up care, supported by weekly visits from a physician. Adherence counselling was provided by primary care counsellors trained in paediatric HIV care. Each visit to a PHC incurs a USD1 fee which is standard throughout Zimbabwe. Cotrimoxazole and ART are provided free of charge through the National ART Programme.

### Participants

Children aged between 6 and 15 years who tested HIV positive through provider-initiated HIV testing and

counselling were enrolled into the cohort study (of whom a proportion were simultaneously enrolled into a randomized controlled trial to assess impact of household support to children living with HIV [trial registry number PACTR201212000442288]), if they chose to access HIV care at the clinic where they were diagnosed and gave consent [23].

### Study procedures

At the initial assessment visit within a week of HIV diagnosis, socio-demographic data, past clinical history and current symptoms were assessed, and a standardized examination performed. Participants underwent WHO Staging and a CD4 count, using Alere Pima™ CD4 machine, was measured [24]. All participants underwent counselling and were started on cotrimoxazole. Participants who screened positive on the WHO TB screen had sputum examined onsite by Ziehl–Neelsen smear microscopy and Xpert TB™ [25]. Participants were seen within 2 weeks of the initial visit to assess adherence and determine side effects of cotrimoxazole, and to commence ART if eligible. The schedule for follow up was based on national guidelines, with visits at 2 and 6 weeks post ART commencement and then on a 3-monthly basis. Participants not eligible for ART at baseline underwent a 3-monthly symptom-based review and examination to reassess ART eligibility. At each visit, a standard proforma was used to collect information on current symptoms, side effects of ART, history of contact with primary healthcare and hospitalization since the previous visit (confirmed by patient-held records) and history of incident infections.

Until February 2014, participants were ART eligible if CD4 was below 350 cells/mm<sup>3</sup> or they had evidence of WHO Stage 3 or 4 infections. ART regimens consisted of stavudine/lamivudine and nevirapine for children under 12 years or tenofovir/lamivudine and nevirapine if over 12 years of age. Efavirenz was substituted for nevirapine in case of concomitant TB treatment or nevirapine allergy. From March 2014, Zimbabwe adopted the WHO 2013 consolidated guidelines with the threshold for ART initiation revised to 500 cells/mm<sup>3</sup> and ART regimes were standardized to zidovudine/lamivudine and nevirapine for those under 12 years and not requiring TB treatment, and tenofovir/lamivudine and efavirenz for those over 12 years of age [26]. CD4 count was performed 6 monthly for all participants. HIV viral load testing was performed at 48 weeks post ART commencement using COBAS Ampliprep/Taqman 48 Version 2.0.

Unscheduled visits were defined as visits occurring outside the scheduled visits for either a medical or non-medical reason (e.g. counselling). Side effects were graded according to the DAIDS grading system [27]. Hospitalization was defined as a participant spending one night or more in a hospital. If a participant had more than one hospitalization, they were counted separately even if related to the same clinical issue. Transfer out was defined as a caregiver informing the clinic of the participant changing care to another clinic and a transfer letter being provided. Participants who failed to attend more than two scheduled

appointments were traced through a phone call and/or a home visit. Participants were defined as having moved away if they had moved care to another clinic without informing clinic staff. Participants were deemed lost to follow-up (LTFU) if they could not be traced. Tracing was performed at clinic level by research nurses who phoned the participant's guardian on 2 occasions if a participant had not returned for a visit within 3 months of the scheduled date. If after the second phone call a participant could not be reached then a voluntary lay health worker visited the house. If a participant died, the cause of death was determined through hospital records. In the case of death occurring outside of hospital, this was confirmed through verbal autopsies with the caregiver.

#### Data management and analysis

Data was extracted from paper forms using optical mark recognition software (Cardiff TELEFORM Intelligent Character, Version 10.7) and analysed using STATA, version 12.1 (STATA Corporation, USA). Stunting and wasting were defined as a height-for-age z-score and a weight-for-age z-score of <-2, respectively [28]. Rates of hospitalization, unscheduled visits and death were calculated. Cox proportional modelling was used to determine the hazard of death, unscheduled visits and hospitalization, controlling for factors found to be significantly associated with the outcome in univariate analysis.

#### Ethical considerations

Written informed consent was obtained from all caregivers and written assent obtained from participants. Ethical approval for the study was obtained from the Medical Research Council of Zimbabwe, the Harare City Health Department Ethics Committee, the Biomedical Research and Training Institute Institutional Review Board and the London School of Hygiene and Tropical Medicine Ethics Committee.

#### Results

A total of 385 participants were enrolled into the study and provided 450 person-years of follow up and a median of 504 days (IQR 1–515). The median age at HIV diagnosis was 11 years (IQR 9–13) and 52% were female. Most participants were infected with HIV through mother-to-child transmission, and 59% were single or double orphans (Table 1). The median CD4 count at HIV diagnosis was 375 cells/mm<sup>3</sup> (IQR 215–599). Over the 18-month period, 296 (77%) participants commenced ART, 70% of whom did so within 4 weeks of enrolment (Table 1). Of the 89 participants who did not initiate ART, 7 were eligible according to national guidelines and 82 were not eligible during follow-up.

At the end of 18 months, 286 (74%) were still in care, 50 (13%) had transferred to another clinic, 12 (3%) moved to another clinic without informing clinic staff, 9(2%) moved away and did not transfer to another clinic, 13 (3%) died, 1 withdrew from the study after initial assessment and 14 (4%) were LTFU (Table 2). Importantly, those who did not

**Table 1. Baseline characteristics of enrolled participants at baseline (n = 385)**

Characteristic	N
Age (years), median (IQR)	11 (9,10,11,12,13)
Female	199 (52%)
Median (IQR), CD4 cells/mm <sup>3</sup>	375 (215–599)
CD4 < 350 cells/mm <sup>3</sup>	177 (46%)
CD4 350–500 cells/mm <sup>3</sup>	74 (19%)
CD4 > 500 cells/mm <sup>3</sup>	131 (34%)
WHO Stage 3 or 4	
Mode of HIV acquisition	155 (40%)
Mother-to-child	369 (96%)
Horizontal	13 (3%)
Unknown	3 (1%)
Orphanhood	157 (41%)
Both parents alive	77 (20%)
Maternal Orphan/Father Alive	71 (18%)
Paternal Orphan/Mother Alive	58 (15%)
Double Orphan	22 (6%)
Unknown status of either parent	
Biological parent as the current caregiver	220 (57%)
Started ART within 4 weeks of enrolment	206 (54%)
Started on ART over 18-month follow up	296 (77%)
Median days on ART for those who initiated (IQR)	485 (359–495)

start ART were significantly more likely to be LTFU than those who started ART ( $p < 0.001$ ). CD4 counts for those who commenced ART increased over the follow-up period, with those who did not start ART ( $n = 89$ ) maintaining their CD4 counts (Figure 1). Of those who commenced ART within 24 weeks of enrolment into the study ( $n = 273$ ), 200 had a viral load sample collected between 40 and 72 weeks post ART, with 195 results obtained. 124 (64%) of those whose viral load result was obtained had a viral load <400 copies/ml.

#### Unscheduled visits

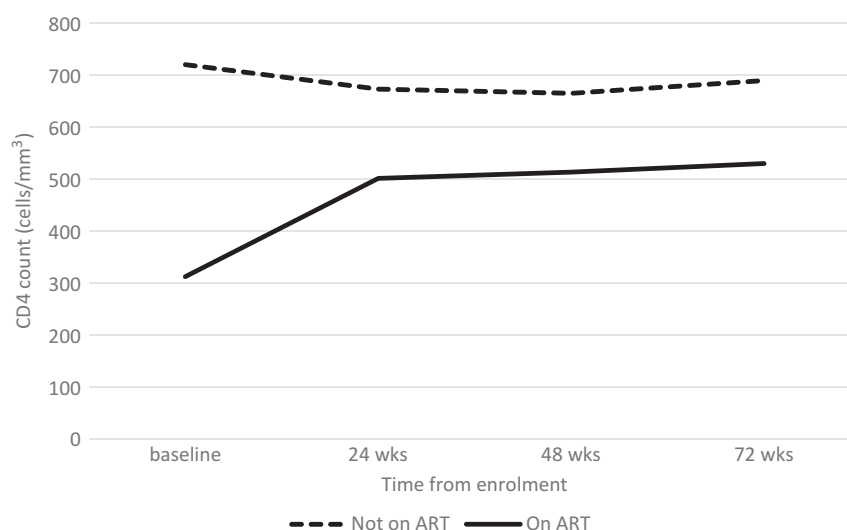
There were 146 unscheduled visits made by 99 participants over the follow-up period, equivalent to a rate of 34.94/100 person years (95% CI 29.70–41.09). Ten unscheduled visits resulted in hospitalization, all of whom were receiving ART. The most common reason for an unscheduled attendance to the clinic was illness ( $n = 133$ , 91%). Other reasons included medication collection ( $n = 5$ , 3%) and additional adherence counselling ( $n = 8$ , 6%). The major cause of illness leading to an unscheduled visit was respiratory tract infection (responsible for 45% of unscheduled visits due to illness), followed by skin infections which accounted for 22% of unscheduled visits due to illness (Table 3).

Side effects from ART resulted in unscheduled visits in 20 patients (15% of unscheduled visits due to illness). Of these, Grade 1 nevirapine hypersensitivity was the most common

**Table 2. Outcomes at 18 months of cohort participants by ART initiation status**

	Total N = 385	Initiated ART over follow up period N = 296	Did not initiate ART over follow up period N = 89	p- value
In care to end of study follow up	286 (74.3%)	243 (82.1%)	43 (48.3%)	<0.01
Planned transferred to another clinic	50 (13.0%)	30 (10.1%)	20 (22.5%)	<0.01
<sup>a</sup> Left area without transfer of care	9 (2.3%)	2 (0.7%)	7 (7.9%)	<0.01
<sup>a</sup> Not in care and untraceable	14 (3.6%)	6 (2.0%)	8 (9.0%)	<0.01
No planned transfer, but was found in care at another clinic	12 (3.1%)	3 (1.0)	9 (10.1)	<0.01
Withdrawn from study	1 (0.3%)	0 (0.0%)	1 (1%)	0.06
Died	13 (3.4%)	12 (4.1%)	1 (1%)	0.18

<sup>a</sup>ascertained through phone calls and home visits.



**Figure 1. Median CD4 count over 18 month follow up by ART status.**

side-effect ( $n = 8$ ). Only one participant was hospitalized due to ART side effects—for rehydration secondary to grade 3 vomiting. Other ART side effects reported at routine 3-monthly follow up were uncommon and self-limiting—consisting of nausea (6%), vomiting (6%), abdominal pain (3%), diarrhoea (6%), fatigue (5%), rash (3%), jaundice (0.1%), dizziness (3%), vivid dreams (2%), and confusion (1%). Overall, side effects of ART resulted in drug switches in 11 cases ( $n = 9$  due to nevirapine hypersensitivity,  $n = 1$  anaemia due to zidovudine and  $n = 1$  grade 3 efavirenz hypersensitivity reaction). Such switches were managed in the primary care clinics by nursing staff with consultation from study physician.

#### Hospitalizations

There were 34 hospitalizations in 27 participants, 9 of which resulted in death. The rate of the hospitalization was 8.14/100 person years (95% CI 5.81–11.39). Lower respiratory tract disease was commonest reason for admission (Table 4). TB was the cause of hospitalization in 8

participants diagnosed through sputum testing using geneXpert or based on chest X-ray findings. Six participants were hospitalized more than once for the same clinical diagnosis (1 admitted twice for HIV-related anaemia, 1 admitted twice for lower respiratory tract infection, 1 admitted twice for Steven Johnson's syndrome secondary to cotrimoxazole due to ongoing symptoms, and 1 admitted thrice for recurrent lower respiratory tract infection). Two participants were admitted twice but for different clinical events. Only three hospitalizations occurred in participants not taking ART, two of which were due to malaria. Only one was HIV related, namely HIV-associated anaemia and thrombocytopenia, and resulted in death. The CD4 count at hospitalization in this participant was 1114 cells/mm<sup>3</sup>.

#### Deaths

The mortality rate was 2.86/100 pyrs (95% CI 1.65–4.95). Of the 13 deaths in the cohort, 12 occurred in hospital and respiratory disease was the most common cause (Table 5).

**Table 3. Reasons for unscheduled visits due to illness (n = 133)**

Cause of unscheduled attendance	N (%)
Respiratory tract infection	60 (45%)
Upper respiratory tract infection	27
Lower respiratory tract infection	16
Pulmonary TB	11
Otitis Media	2
Tonsillitis	4
Skin infections	29 (22%)
Oro-labial Herpes Simplex	5
Herpes Zoster	5
Chicken Pox	1
Bacterial skin infection	15
Fungal skin infection ( <i>Tinea capitis</i> or <i>corporis</i> )	2
Papular pruritic eruption	1
Gastrointestinal disease	16 (12%)
Gastroenteritis	9
Chronic diarrhoea	2
Hepatitis A	1
Oral candidiasis	3
Oesophageal candidiasis	1
Antiretroviral therapy side effects	20 (15%)
Grade 1 Nevirapine hypersensitivity	8
Grade 2/3 NNRTI skin hypersensitivity	8
Grade 2/3 vomiting	3
Anaemia	1
Miscellaneous	8 (6%)
Minor trauma	1
Gingivitis	2
Conjunctivitis	2
Mumps	1
TB lymphadenitis	2

The median CD4 count at enrolment of those who died was 73 cells/mm<sup>3</sup> (IQR 12–205) and 77% of those who died had WHO Stage 3 or 4 disease at enrolment. The median time from enrolment to death was 76 days (IQR 59–410).

A CD4 count less than 350 cells/mm<sup>3</sup> at enrolment, WHO stage 3 or 4 HIV disease and wasting were associated with hospitalization and death on univariate analysis (Table 6). CD4 count less than 350 cells/mm<sup>3</sup> and advanced WHO stage remained significantly associated with the outcome in multivariate analysis for hazard of hospitalization (aHR 3.6 (95%CI 1.6–8.2), aHR 2.6 (95% CI 1.1–6.2)), no variables remained significantly associated with the hazard of death. Being older (HR 2.1 (95%CI 1.4–3.1), WHO stage 3 or 4 disease (HR 1.5 (95% CI 1.0–2.1) and wasting (HR 1.8 (95% CI 1.3–2.7)) were associated with having unscheduled visits due to illness. On multivariate analysis, association with being in an older age group (aHR 1.9 (95%CI 1.3–3.1)) and wasting (aHR 1.8 (95%CI 1.0–2.3)) remained significant.

**Table 4. Causes of hospitalization (n = 34)**

Cause of hospitalization	N (%)
Respiratory Illness	n = 18 (53%)
Pulmonary TB	7
Disseminated TB	1
Lower respiratory tract infection	9
<i>Pneumocystis jiroveci</i> pneumonia	1
Neurological Illness	n = 5 (15%)
Bacterial meningitis	1
Cryptococcal meningitis	2
CNS lymphoma	1
Seizure (cause unknown)	1
Miscellaneous	n = 11 (32%)
Hyperglycaemia	1
Anaemia <sup>a</sup>	3
Congestive Cardiac Failure	1
Gastroenteritis	1
Vomiting Secondary to ART	1
Malaria <sup>b</sup>	2
Stevens–Johnson syndrome secondary to cotrimoxazole	2

Numbers refer to hospitalization events rather than numbers of participants admitted, <sup>a</sup>n = 1 not on ART, <sup>b</sup> n = 2 not on ART

**Table 5. Causes of death amongst cohort participants over 18 month follow up (n = 13)**

Cause of death n (%)	
Pulmonary TB	4 (31)
Lower respiratory tract infection	4 (31)
Malignancy – CNS lymphoma	1 (7)
Congestive cardiac failure	1 (7)
Meningitis	1 (7)
Accidental drowning	1 (7)
Anaemia/Thrombocytopenia	1 (7)

## Discussion

Our study demonstrated that nurse-led HIV care for children and adolescents is possible in primary care settings. The rate of retention in care was comparable to that reported in facility-based settings and higher than a recent retrospective cohort review of children attending decentralized care in Swaziland [20,29]. Provision of HIV care in primary care facilities reduces the distance that patients need to travel to access treatment, and this may help improve retention in care [3,20]. Notably, the rate of retention in care was significantly lower in those who did not start ART, with half of those who did not initiate ART being LTFU. This finding has been reported previously and may be because patients perceive no benefit in attending for care if they are not

**Table 6. Cox proportional hazard ratio for hospitalization, unscheduled visit due to illness and death**

	Hospitalization N = 34						Unscheduled visit N = 118				Death N = 13			
	Total	N	Rate (95% CI)	Crude hazard			N	Rate (95% CI)	Crude hazard		N	Rate (95% CI)	Crude hazard	
				ratio	AHR <sup>a</sup>				ratio	AHR <sup>a</sup>			ratio	AHR <sup>a</sup>
Age	<b>11–15</b>	200	17	7.7 (4.8–12.5)	0.9 (0.5–1.8)	-	82	37.3 (30.1–46.4)	2.1 (1.4–3.1)	1.9 (1.3–2.9)	7	3.0 (1.4–6.2)	1.1 (0.4–3.3)	-
	<b>6–10</b>	185	17	8.6 (5.3–13.8)	1		36	18.2 (13.1–25.2)	1		6	2.8 (1.2–6.1)	1	
Sex	<b>Female</b>	199	15	6.9 (4.2–11.5)	0.7 (0.4–1.4)	-	68	31.4 (24.7–39.8)	1.3 (0.9–1.8)	-	9	3.8 (2.0–7.4)	1.6 (0.5–5.5)	-
	<b>Male</b>	186	19	9.44 (6.0–14.8)	1		50	24.9 (18.8–32.8)	1		4	1.8 (0.68–4.9)	1	
CD4 at enrolment <sup>b</sup>	<b>&lt;350</b>	177	26	13.1 (8.9–19.3)	4.1 (1.8–9.4)	3.6 (1.6–8.3)	65	32.8 (25.7–41.8)	1.4 (0.9–1.9)	-	11	5.2 (2.9–9.3)	5.0 (1.1–23.1)	4.2 (0.9–19.8)
	<b>&gt;350</b>	205	7	3.2 (1.5–6.8)	1		53	24.5 (18.7–32.0)	1		2	0.8 (0.2–3.4)	1	
WHO stage	<b>3–4</b>	155	25	14.8 (10.0–21.9)	4.0 (1.9–8.6)	2.6 (1.1–6.2)	59	34.9 (27.1–45.1)	1.5 (1.0–2.1)	1.2 (0.8–1.9)	10	5.4 (2.9–10.0)	4.1 (1.1–15.2)	2.5 (0.6–10.7)
	<b>1–2</b>	230	9	3.6 (1.9–6.9)	1		59	23.7 (18.4–30.6)	1		3	1.1 (0.3–3.5)	1	
ART within 4 weeks	<b>Y</b>	206	22	9.2 (6.1–14.0)	1.4 (0.7–2.9)	-	69	28.9 (22.8–36.5)	1.1 (0.75–1.6)	-	10	3.9 (2.1–7.3)	2.1 (0.6–7.9)	-
	<b>N</b>	179	12	6.7 (3.8–11.8)	1		49	27.3 (20.0–36.6)	1		3	1.5 (0.5–4.7)	1	
Stunting	<b>Y</b>	91	13	13.0 (7.5–22.4)	1.9 (1.0–3.8)	-	31	31.0 (21.8–44.1)	1.1 (0.74–1.7)	-	4	3.7 (1.4–9.9)	1.8 (0.45–6.0)	-
	<b>N</b>	294	21	6.6 (4.3–10.1)	1		87	27.4 (22.2–33.8)	1		9	2.6 (1.4–5.0)	1	
Wasting	<b>Y</b>	105	19	17.3 (11.1–27.2)	3.5 (1.8–6.8)	2.1 (1.0–4.5)	47	42.9 (32.2–57.1)	1.8 (1.3–2.7)	1.5 (1.0–2.3)	7	5.9 (2.8–12.4)	4.7 (1.4–16.2)	2.7 (0.7–10.6)
	<b>N</b>	280	15	4.9 (2.9–8.1)	1		71	23.0 (18.3–29.1)			6	1.8 (0.8–4.0)	1	

<sup>a</sup>Adjusted for factors significantly associated with the outcome in univariate analysis; AHR: adjusted hazard ratio; <sup>b</sup> data missing for n = 3

receiving treatment [30,31]. The 2015 WHO guidelines recommend initiation of ART regardless of disease stage or age and this may facilitate retention in care [32].

Worryingly, only two-thirds of children achieved virological suppression after starting ART, similar to the proportion reported in a recent study in a clinic in a central hospital in Harare [33]. Other studies have demonstrated virological suppression rates ranging from 27 to 89% in adolescents [34]. Notably, 172 (44.7%) of our study cohort received community lay worker support due to participation in a randomized controlled trial which may have potentially increased the proportion of participants with viral load suppression. There were no drug-stock outs over the duration of our study and so the virological unsuppressed rate most likely reflects suboptimal adherence. Since study completion, viral load testing has become available at primary care clinics within Zimbabwe's health service. Children are expected to take ART for at least two decades longer than adults and the need for interventions in this age-group to support sustained adherence to minimize emergence of drug resistance cannot be over-emphasized, particularly in resource-limited settings where options for second and third-line ART are limited.

Despite a good immunological response to treatment, a high frequency of PHC attendances occurred outside scheduled clinic appointments. Most unscheduled presentations were, however, due to minor illness and were managed at primary care level, with only a minority resulting in referral to hospital for further management. Such referrals were decided on due to the nature of the limited services primary care health facilities are able to provide in the event of more serious illness. Decentralized HIV care therefore provides a system for triage and reduces the burden on secondary health facilities, making it a sustainable system for chronic care provision.

The leading cause of unscheduled visits, hospitalization and death was respiratory tract infections, even among patients on ART. We have previously reported a high burden of chronic lung disease in perinatally infected children and adolescents, which is associated with considerable morbidity including recurrent respiratory tract infections, poor lung function and reduced exercise tolerance [35]. The recurrent respiratory tract infections observed in this study may be due to underlying chronic lung disease. The pathogenesis is poorly understood but is thought to be a sequela of chronic infections and/or HIV-mediated chronic inflammation. Once established chronic lung disease appears to be poorly responsive to ART, and children with recurrent respiratory tract infections may require further interventions such as additional prophylactic antibiotics or anti-inflammatory agents [36].

Notably, 8 hospitalizations were TB related, 4 of them resulting in death, despite active case finding at baseline through sputum testing and at follow up through WHO symptom screening. This demonstrates the low sensitivity of the WHO TB screening tool, and reflects the paucibacillary nature of TB in children. TB preventative therapy using isoniazid prophylaxis had not been widely implemented in Zimbabwe at commencement of the study and no

participant received it over the study period. Skin disease was the second most common cause of unscheduled visits to PHCs. Recurrent skin infections are strongly associated with HIV infection in children, and in high HIV prevalence settings should prompt HIV testing [37,38]. Side effects of ART accounted for only 15% of unscheduled attendances. Importantly, most patients with side effects were managed in primary care necessitating few drug switches, all effected at primary care level.

As has been reported in other studies, advanced disease stage and immunosuppression were risk factors for both hospitalization and death [39,40]. The median CD4 count at diagnosis was 375 cells/mm<sup>3</sup>, and the median age at diagnosis in a cohort where nearly all participants were infected perinatally was 11 years, implying an average delay of a decade in diagnosing HIV infection. Given the high HIV-associated mortality observed in infants, there is limited awareness that a third of HIV-infected infants survive to adolescence even without treatment [41]. Therefore, HIV testing is only offered when children present with conditions indicative of HIV infection, by which time they have often developed advanced disease [19,29]. However, at least a quarter of children retained high CD4 counts (>500 cells/mm<sup>3</sup>) and remained ineligible for ART based on current national guidelines. While a sub-group of these may be true long-term non-progressors or elite controllers, many remain pauci-symptomatic and may not prompt healthcare workers to offer HIV testing [33,34].

Older age was associated with more frequent unscheduled visits but not death and hospitalization. This might reflect a combination of survival bias and longer life-time exposure of uncontrolled viremia. While these children survived into adolescence without major illness, the uncontrolled viremia may have resulted in a higher prevalence and more prominent chronic disease phenotype such as chronic lung disease.

The strengths of the study were the prospective design and that participants were actively followed up to ascertain outcomes. Detailed clinical data were collected to establish the reasons for visits to health facilities and cause of death. The study was conducted in public sector services and therefore the findings are broadly generalizable. Limitations include the lack of viral load data in all participants (73% of those eligible had viral load measured). There is a risk that the Cox proportional hazard models for death and admission may be over-fitted due to a small number of events. To mitigate this risk, no variables were specified a priori. Diagnoses such as respiratory tract infections were made in PHC were based on symptoms and clinical examination, as diagnostic facilities are limited.

## Conclusions

Our study shows that decentralized nurse-led HIV care for children is possible and results in clinical outcomes comparable to those reported in children elsewhere in southern Africa [20]. Implementation of 2015 WHO guidelines that recommend universal treatment of all HIV-infected individuals, is likely to result in a substantial increase in children eligible for treatment, particularly given the current low ART coverage. Considerable investment in age-appropriate HIV

testing strategies, training and support for primary health care providers and interventions to support adherence need to be strengthened to achieve universal access and optimum treatment outcomes among children and adolescents.

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#### Competing Interests

The authors have no conflict of interests

#### Author's Contributions

RAF designed the study. GMCH and ED supervised data collection. GMCH and VS analysed the data. GMCH wrote the first draft of the manuscript. All authors contributed to the writing of the manuscript.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no conflict of interest.

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