Rural Realities in Paediatric HIV Service Delivery

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Electronic version

Lay-out by Janneke H van Dijk

Photos were taken within the hospital's catchment area, not depicting persons related to the study or HIV clinic

Rural Realities in Paediatric HIV Service Delivery

De praktijk van rurale, paediatrische HIV-dienstverlening

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Rebekah G. Lyndon
Sandra Chishimba

For the Macha community

In loving memory of my sister Ada H. Lyndon – van Dijk

Contents:


KENYA
TANZANIA
MALAWI
ZAMBIA
ZIMBABWE
NAMIBIA
BOTSWANA
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southern africa

Part One: Introduction

Chapter 1

General Introduction and outline of the thesis

Sub-Saharan Africa is the most heavily affected region in the global human immunodeficiency virus (HIV) epidemic, with nearly 1 in every 20 adults (4.9%) living with HIV and accounting for 69% of the people living with HIV worldwide. In 2011, an estimated **23.5 million** [22.1-24.8 million] **people living with HIV** resided **in sub-Saharan Africa** [1]**.**

HIV in Africa is a *generalized* epidemic – implying that the HIV infection is not restricted to high risk groups like sex workers, men who have sex with men (MSMs), people who inject drugs etc. but has penetrated into the general population. It involves whole families or some of the family members. It is a disease of young and old. By now HIV is a chronic disease, touching on many different aspects of life, and development stages.

Over the last 30 years, since the first cases of what is now recognized as HIV infection were identified in 1981, the rise of the number of HIV-infected women of childbearing age in developing countries resulted in the increased number of children infected with HIV. During the past decade, many national HIV epidemics have changed dramatically. Although HIV remains one of the world's most serious health challenges, global solidarity in the HIV response during the past decade continues to generate health gains.
In 2011, **92% of pregnant women living with HIV resided in sub-Saharan Africa**, but the majority of countries continue to achieve dramatic results in the AIDS response – in lives saved and new infections averted. The percentage of pregnant women living with HIV who received antiretroviral therapy or prophylaxis is now 59% [53–66%] and the number of children *newly infected* fell by 24% from 2009 to 2011 [1]. In these three years, antiretroviral prophylaxis prevented 409 000 children from acquiring HIV infection in low- and middle-income countries. Still, recent estimates from UNAIDS are that **worldwide** an estimated **3.4 million children younger than 15 years of age are infected with HIV** [2]**,** about 91% of whom reside in Africa. With that Sub-Saharan Africa is the epicenter of the pediatric HIV epidemic.

The scaling up of antiretroviral therapy in low- and middle-income countries has transformed national AIDS responses and generated broad-based health gains. In countries with generalized epidemics that account for the overwhelming majority of the children newly infected, major gains have occurred during the past decade. **Zambia** is among the few countries in the African region that achieved encouraging progress in their HIV response. While in 2011 coverage of services to prevent mother-to-child transmission (PMTCT) of HIV in sub-Saharan Africa reached 59%, Zambia was among the six countries in the region that **achieved a PMTCT coverage of more than 75%** [1].
Zambia was also among the 6 sub-Saharan African countries where between 2009 and 2011 the **number of children newly infected with HIV declined by 40-59%**, compared to the overall reduction of 24% in sub-Saharan countries. This is a combined effect of decreasing incidence in women and the introduction of the PMTCT program. In Zambia, the estimated number of new infections in infants and children aged 1-4 years was 2,946 in 2011 [3].
In 2011, an estimated 56% of people eligible for HIV treatment in sub-Saharan Africa received it – compared to a global average of 54%. Five countries in the region had **achieved more than 80% coverage of HIV treatment**, among which was Zambia [1]. However, the estimated coverage is much lower **among children aged 0-14 years (28.1%)** than among adults 15 years and older (90%) [3]. Tremendous effort is required on them just as on adults.

Although much of the news on HIV/AIDS is encouraging, challenges remain. Despite the gains, HIV/AIDS is affecting the health and welfare of children and undermining hard-won gains in child survival in some highly affected countries [4]. **Sub-Saharan Africa** still **accounted for 71% of the adults and children newly infected in 2011**, underscoring the importance of continuing and strengthening HIV prevention efforts in the region.

The Macha setting

Macha is a rural village situated in the Southern Province of Zambia, approximately 70 km from the nearest town of Choma and 350 km by road from the capital city of Lusaka.
Macha Mission Hospital was established in 1957. The 208-bed hospital is administered by the Zambian Brethren in Christ Church that functions within the healthcare system of the Ministry of Health. Macha Hospital serves as a referral hospital for at least 13 rural health centers, bringing patients in from an 80 km radius. The catchment area of Macha Hospital is populated by traditional villagers living in small, scattered homesteads, characteristic of much of rural sub-Saharan Africa, with an estimated population size of over 150,000 persons. Overall population density in this area is 25 per km^2 and roughly 50% of the population is under 12 years of age [5]. Other specific data for the local population are not reliable, but country-wide the crude birth rate is 45.6 per 1,000 population, with an infant mortality of 68.9 per 1,000 live births, and an under-5 mortality of 111 per 1,000 live births. Average life expectancy at birth is 48.5 years, and the HIV prevalence among the population aged 15-49 years is 13.5% [6].

An important development for healthcare in Macha was the establishment of the Malaria Institute at Macha (MIAM) in 2003, officially opened in 2005. Whereas initial research focused on malaria, soon the institute expanded it's range of activities further to Tuberculosis and HIV/AIDS related research and programs, and changed the name into Macha Research Trust (MRT). The Macha Research Trust is a unique place - both in the sense that it is one of the few research institutes in sub-Saharan Africa established in a remote rural area and is in the midst of an area traditionally endemic to malaria, HIV and tuberculosis. A relationship with the Erasmus Medical Center was established in 2005 and is primarily focused on research, education, and training. Erasmus MC provided sponsorship for the construction and development of a new Clinical Research Laboratory at Macha, which is fully operational since the end of 2011.

Implementation of HIV services

Antiretroviral treatment (ART) provision at the hospital became available in 2005, through the Government of Zambia's antiretroviral treatment program, with additional support from the President's Emergency Plan for AIDS Relief (PEPFAR) through the non- governmental organization, AIDSRelief. Since then over 8,000 patients are enrolled in HIV care, and over 4,000 patients started on ART.

HIV/AIDS is not just a health issue but also *a development issue*. Its impact extends well beyond typical health indicators (e.g. infant mortality rate, life expectancy and death rate) to key development indicators (e.g. per capita income, literacy and GDP growth rates) [7]. Successful antiretroviral treatment programs in rural sub-Saharan Africa face different challenges than programs in urban areas. Although the level of the epidemic in rural areas is lower than in urban areas, the population affected is quite high since about 65 per cent of the population lives there. At

this stage of dealing with the epidemic, lessons have been learnt and capacities have been improved - both in terms of human resources and institutional capacities for a multi-sectorial approach of interventions. The generalized HIV epidemic in Zambia is such that all prongs of interventions should be at full scale, and half measures in some areas would cause little overall impact to be made in reversing the epidemic. The availability of clinical management resources as well as the application of prevention, diagnosis and treatment standards are necessary to reach that goal.
Besides our scientific knowledge, appropriate service delivery requires understanding of the local situation clients are in, and it's complexity. Treating HIV in a rural African setting requires holistic care, addressing the different aspects involved. It requires a continuum of care. For sustained and holistic action against HIV/AIDS, it is essential that the community is involved and takes up a proactive role. Efforts are made to integrated HIV related services so as to simplify the process of accessing services, reduce stigma, and *normalize HIV into the health sector* [7].

HIV service delivery to adults is challenging due to social, logistical and personal factors, but among children this is further complicated by their partial or complete dependence on caregivers.
In 2007, Drs. William Moss (John's Hopkins University, School of Public Health, Baltimore, USA), and Janneke van Dijk (Macha Research Trust, Zambia) initiated the paediatric ART (PART) study, a prospective cohort study of HIV-infected children cared for by the HIV clinic at Macha Hospital, and one of the longest established cohorts of primarily perinatally HIV-infected children in rural sub-Saharan Africa.

Aim and outline of this thesis

With the few paediatric HIV programs and studies reporting from rural areas, the aim of this thesis is to evaluate HIV service delivery in rural Zambia and focus on the factors influencing the care and treatment of HIV-1 infected children.

The first part of this thesis reviews available, data on paediatric treatment programs of Sub-Saharan Africa [**Part one**, *chapter 2*]. In this chapter, we review the effectiveness of paediatric antiretroviral treatment programmes in sub-Saharan Africa and discuss the implications of these findings for the care and treatment of HIV-infected children in this region. Our review of the published literature showed that children in sub-Saharan Africa achieved comparable outcomes to those in high-income settings although they enrolled in care at older ages and more advanced stages of disease. The findings emphasised the need for low-cost diagnostic tests that allow for earlier identification of HIV infection in infants living in sub-Saharan Africa, improved access to antiretroviral treatment programmes, including expansion of care into rural areas, and the integration of antiretroviral treatment programmes with other health-care services, such as nutritional support.

Programs providing paediatric ART in sub-Saharan Africa face many challenges, many of which are exacerbated in rural areas. In the following chapters [**Part two**, *chapters 3 and 4*] we look at issues specifically related to the population in rural southern Zambia. Our observations highlight barriers to the care of HIV-infected children unique to rural settings, specifically long travel times and lack of transportation, but are encouraging in that age at clinic enrolment and immunologic outcomes in the first year of treatment did not differ substantially from published reports on the care of HIV-infected children in urban sub-Saharan Africa. These findings suggest that the barriers to the care of HIV-infected children in rural settings do not pose insurmountable obstacles to desirable treatment

outcomes. Despite these barriers, children in rural Zambia had a substantial rise in CD4+ T cell counts in the first year of ART although longer follow-up is needed to indicate if these gains can be sustained.

Part three, *chapters 5 and 6*, reviews treatment responses in the study population in rural Zambia. HIV-infected children receiving treatment in this rural clinic experienced sustained immunologic and virologic improvements. Children with longer travel times were less likely to achieve virologic suppression, supporting the need for decentralized models of ART delivery.
It has been shown that deficits in growth observed in HIV-infected children in resource-poor settings can be reversed with antiretroviral treatment. However, many of these studies have been conducted in urban areas with older paediatric populations. Additional analyses were undertaken to evaluate growth patterns after ART initiation in this young paediatric population in rural Zambia with a high prevalence of undernutrition, and identify characteristics at ART initiation that influence growth trajectories.

In **part four,** issues regarding HIV service delivery are addressed. We reviewed mortality rates and clinical predictors of mortality during the period prior to ART initiation [*chapter 7*], underscoring the need to increase efforts to identify HIV-infected children at an earlier age and stage of disease progression.
Antiretroviral treatment options for young children co-infected with HIV and tuberculosis are limited in resource-poor settings in sub-Saharan Africa, where the dual burden of HIV infection and tuberculosis represents a significant threat to the health of children. Using available pharmacokinetic data, an efavirenz (EFV) dosing schedule was developed for young co-infected children and implemented as the standard of care at Macha Hospital in Zambia. Treatment outcomes in children younger than 3 years of age or weighing less than 10 kg receiving either an EFV-based ART plus anti-tuberculous treatment or nevirapine-based (NVP) ART were compared, and are presented in *chapter 8.*
Repeatedly decentralization is mentioned as one of the strategies to scaling-up access to antiretroviral treatment, but few such programs have been evaluated. We compared outcomes for children receiving care in mobile and hospital-based HIV clinics in rural Zambia [*chapter 9*]. In *chapter 10,* we describe the feasibility and challenges in providing antiretroviral treatment to children in Sub-Saharan Africa, highlighting some of the successful practices and developments in service delivery and care.

To conclude, **part five** *chapter 11* offers a discussion of our main findings in the context of the present literature.

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Chapter 2

Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa

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Abstract

Assessment of antiretroviral treatment programmes for HIV-infected children in sub-Saharan Africa is important to enable the development of effective care and improve treatment outcomes.

We review the effectiveness of paediatric antiretroviral treatment programmes in sub-Saharan Africa and discuss the implications of these findings for the care and treatment of HIV-infected children in this region.

Available reports indicate that programmes in sub-Saharan Africa achieve treatment outcomes similar to those in North America and Europe. However, progress in several areas is required to improve the care of HIV-infected children in sub-Saharan Africa.

The findings emphasise the need for low-cost diagnostic tests that allow for earlier identification of HIV infection in infants living in sub-Saharan Africa, improved access to antiretroviral treatment programmes, including expansion of care into rural areas, and the integration of antiretroviral treatment programmes with other health-care services, such as nutritional support.

Introduction

Sub-Saharan Africa is the epicentre of the HIV pandemic and is home to an estimated 2 million HIV-infected children aged under 15 years, representing 90% of all HIV-infected children globally [1]. Without treatment, more than one-third of these children will not survive past their first birthday [2]. In 2003, WHO launched the 3 by 5 Initiative and mobilised resources to increase access to effective antiretroviral therapy in resource-poor settings to reduce morbidity and mortality caused by HIV. Substantial improvements have been made in sub-Saharan Africa for adults, with the estimated 100 000 people receiving antiretroviral therapy in 2003, increasing to more than 1.3 million in 2006 [3]. Despite this success, progress has been uneven and coverage for children has lagged behind [4].

Antiretroviral therapy programmes face many obstacles in sub-Saharan Africa. These include a lack of trained physicians and other health-care workers available to provide antiretroviral therapy, poorly developed drug procurement and distribution systems [5,6], and unaffordable assays for monitoring response to therapy (particularly HIV-1 viral load) and medication side-effects. These obstacles can be even more challenging in the provision of care to HIV-infected children. The diagnosis of HIV infection in infancy requires a higher level of technology than is currently available in most resource-poor settings; paediatric drug formulations are not widely available; health-care personnel are scarce and often untrained in the treatment, adherence monitoring, or counselling of HIV-infected children; and many health-care facilities have not developed policies and protocols to care for HIV-infected children [7,8].

Reports on the initial experiences of treatment programmes for HIV-infected children are beginning to emerge from sub-Saharan Africa and their evaluation is crucial to overcoming obstacles and improving the care of HIV-infected children. We review the effectiveness of paediatric antiretroviral therapy programmes in sub-Saharan Africa, specifically treatment outcomes, adherence, and mortality, and discuss the implications of these findings to improve the care of HIV-infected children in this region.

Methods

We searched the online databases PubMed and Web of Science for articles published in English before Oct 1, 2007, with the following terms: “HIV” AND “Africa” AND “antiretroviral” AND (“treatment” or “therapy”) AND (“pediatric” or “child”). Subject headings (PubMed only), titles, and abstracts were searched. The search identified 258 potential articles from PubMed and 133 from Web of Science. Titles and abstracts were reviewed to identify eligible articles. Articles were eligible (1) if they included HIV-1-infected children from programmes in west Africa or HIV-infected children from programmes in east and southern Africa where HIV-1 is predominant; and (2) if results were reported on clinical, immunological, or virological outcomes, adherence, or adverse events from studies of treatment-naive children. Reports of clinical trials, special populations of children, such as children in intensive care units, children with tuberculosis, children within specific age-groups, or programmes in which outcomes for children were not reported separately from those of adults were not included. 21 articles fulfilled the inclusion criteria [9-29]. Review of the citations within these articles yielded an additional two articles [30,31].

Because the treatment of children in sub-Saharan Africa is recent, abstracts from the 2004 and 2006 International AIDS Conferences, the 2007 Conference on Retroviruses and Opportunistic Infections, and the 2007 International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention were also searched (details of this search are in the webappendix). These searches yielded 48 abstracts [32-79], although one was subsequently excluded because most children were not treatment naïve [77].

If several abstracts and published articles reported results from the same cohort or treatment programme, the most recent published article or abstract (if only abstracts were available) was used. If relevant information was not available from these sources, or separate reports were available on specific topics, such as adherence or adverse reactions, articles or abstracts from previous years were used. In general, abstracts provided less information than published papers and reported preliminary results. To determine whether the information obtained from abstracts altered our conclusions, we repeated the analysis using only published reports. The findings were unchanged and we present our analyses with both abstracts and published articles.

Table 1. Antiretroviral treatment programs for children in sub-Saharan Africa reporting characteristics at initiation and treatment outcomes

	Location, time frame	Median duration of follow-up	N (% male)	Age at entry	Definition of paediatric age	CD4 % at entry	Viral load (log$_{10}$ copies/mL) at entry	Drug regimens	Mortality	Lost to follow-up
Published studies										
ANRS 1244 and 1278 [9,10]	Abidjan, Cote d'Ivoire 2000-2004	3 years	76 (56%)	Med: 6·5 yrs Range: 0·7-15·2 yrs <2 y: 5%	—	Median 7.5% (IQR 2.1-11.1%); 385 with < 5%	Median 5.37 (IQR 5.07-5.99)	2 NRTI with either EFV or nelfinavir; didanosine, Kaletra also available	9 deaths (12%); 88% survival at 36 months, 86% survival at 42 months	4 (5%)
AMPATH clinics [11, 12, 13]	Eldoret, Kenya 2002-2005	34 weeks	279 (51%)	Med: 6 yrs 95%CI: 6·8m13·7yrs <12 m: 7·4%	—	Median 9% (95% CI 1-38%)		AZT/ D4T, 3TC, NVP	10 deaths (4%)	32 (11%)
Kenyatta National Hospital	Nairobi, Kenya 2004-2005	9 months	67 (51%)	Med: 4·4 yrs IQR: 2.4-6.0 <18 m: 0%	18 m-12 yrs	Median 6.2% (IQR 3.6-10.3%) 82% with < 15%	Median 6.1 (IQR 5.5-6.5)	AZT/ D4T, 3TC, EFV; D4T, 3TC, NVP (adult FDC combination); ABC and nelfinavir also available	6 deaths (5%)	—
Ble et al	Dodoma, Tanzania 2002-2005	12 months	59 (66%)	Med: 53·8 m Range: 7·127 m <12 m: 5·1%	—	Median 9.6% (range 0-27.6%)	—	AZT, 3TC, NVP/ nelfinavir	—	—
Multisite Medecins Sans Frontiere project	Cambodia, Kenya, Malawi, Mozambique, Thailand, Uganda, Burkina Faso, Zimbabwe 2001-2005	6 months	1184 (52%)	Med: 7 yrs IQR: 4·6·9·3 yrs <18 m: 1%	0-13 yrs	Median 9.9% for <5 yrs (IQR 6-13.2%); 85.3% with <15%; median 190x 10^9/L for 5-13 yrs (IQR 73-339x 10^9/L); 51% with <200x10^{9} [1]		D4T, 3TC, NVP (adult fixed-dose combination); AZT, EFV, didanosine and a PI were also available	36 deaths (3%); 95% survival at 12 months	89 (8%), 1 (0.1%) transferred, 15 (1%) stopped therapy, 31 (3%) unknown outcomes
DREAM program	Mozambique 2002-2004	1 year	297	Mean: 5·1 yrs (SD: 3·2)	—	56.4% with <15%	55.3% >5.0	AZT/ D4T, 3TC, NVP; D4T, 3TC, NVP (adult FDC); ABC and nelfinavir also available	28 deaths (9%)	9 (3%)
Walker et al	Lusaka, Zambia 2004-2006	6 months	76	Med: 8·1 yrs	1-14 yrs	Median 6% (IQR 3-9%); 36% with <5%	—	AZT/ D4T, 3TC, NVP; D4T, 3TC, NVP (adult FDC)	6 deaths (8%)	—
Red Cross Children's Hospital	Cape Town, South Africa 2002-2004	1 year	409 (55%)	Med: 23 m IQR: 8·9-54·6 m <2 yrs: 50·6%	—	Median 11.7% (IQR 7·17.3%); 66.2% with <15%	Median 5.6 (IQR 5.1-6.1) 30.2% >6.0	D4T, 3TC, EFV/ ritonavir	63 deaths (15%); 84% survival at 12 months	19 (5%),86 (11%) transferred, 12 (3%) stopped therapy

	Location, time frame	Median duration of follow-up	N (% male)	Age at entry	Definition of paediatric age	CD4 % at entry	Viral load (log_{10} copies/mL) at entry	Drug regimens	Mortality	Lost to follow-up
Reddi et al	KwaZulu-Natal, South Africa 2003-2005	8 months	151 (49%)	Med: 5-7 yrs Range: 0·3-15·4 yrs <li yrs: 25·8%	0-15 yrs	Median 7.4% (IQR 2.1%-13.7%); 35.6% with <5%	—	D4T, 3TC, or AZT, didanosine, plus EFV, NVP, Kaletra, ritonavir	13 deaths (8.6%) 91% survival at 12 months	0 (0%); 1 (0.7%) transferred
Jooste et al	Northern Cape, South Africa 2003-2004	6 months	100	Mean: 66 m Range: 3 m-13 yrs	—	96% with <15%; 28% with <5%	82% >5.0	D4T, AZT, NVP/ EFV/ lopinavir+ritonavir; ABC, didanosine also available	9 deaths (9%)	
Abstracts										
Nkengasong et al	Abidjan, Cote d'Ivoire			Med: 7 y <6 y: 25%	—		Median 5.6	—		
Mahan et al	Abidjan, Cote d'Ivoire				—			AZT/ D4T, 3TC, EFV/ NVP/ nelfinavir		
Kline et al (Multisite BIPAI project)	Botswana, Uganda, Lesotho, Swaziland, Malawi			Mean: 5·1-7·8 y	—			—		
Carter et al (Multisite MTCT-plus initiative)	9 African countries			Med: 19 m Range: 2 m-11 y <12m: 39%	—			AZT/ D4T, 3TC, NNRTI/NRTI/PI		
Warren et al	Addis Ababa, Ethiopia				—			—		
Kamya et al	Kampala, Uganda				0-18 yrs			AZT/ D4T, 3TC, EFV/ NVP		
Nannyonga Musoke et al	Kampala, Uganda			Mean: 9·4 y Range: 2·18 y	—			2 NRTI and either a NNRTI or PI		
Ajuna et al	Kampala, Uganda			Med: 5 y IQR: 1-12 y	—		Median 5.5 (IQR 2.3-5.9)	D4T, 3TC, NVP (adult FDC)		
The Mildmay Centre	Kampala, Uganda			Med: 8 y Range: 9 m-12 y	0-13 yrs			—		
Alexander et al	Eastern Uganda			Med: 4 y Range: 3 m-15 y	—		0% < 50 copies/mL	AZT, 3TC, NVP; lopinavir+ritonivir also available		
Ahoua et al	North-Western Uganda			Med: 5.4 & 5.5	—			2 NRTI plus 1 NNRTI; didanosine, tenofovir, ABC and Kaletra also available		
Kariyo et al	Bujumbura, Burundi			Mean: 6·2 y	0-15 yrs			2 NRTI plus 1 NNRTI; didanosine also available		
Weigel et al	Lilongwe, Malawi			Med: 8 y Range: 0·4-12·5 y	—			AZT/ D4T, 3TC, NVP		
Botswana-Baylor Children's Clinical Centre for Excellence	Gaborone, Botswana			Med: 5 y	—		Median 5.6 38.6% >5.9	AZT/ D4T, 3TC, NVP/ EFV		

Mbewe et al	Lusaka, Zambia	Med: 6·5 y	---		AZT/ D4T, 3TC, NVP/ EFV
KwaZulu Natal	KwaZulu Natal, South Africa		---		---
Archary et al	Durban, South Africa	Mean: 5·9 y Range: 1-13 y <3 y: 21%	---	Mean 5.71 (range 3.6-7.0)	D4T 3TC, EFV/ Kaletra
Moultrie and Meyers	Soweto, South Africa	Med: 3·4 y	---		2 NRTIs plus 1 NNRTI; didanosine and PIs available
Coetzee et al	Cape Town, South Africa	Med: 4·3 y	---	Median 5.0 (IQR 4.3-5.5)	AZT/ D4T, 3TC, EFV/ NVP
White et al	Lesotho	Med: 7 y Range: 3m -14 y	0-14 yrs		---

Includes the 30 studies of treatment programmes that reported immunological or virological treatment outcomes. Information from additional studies was primarily used in assessing adherence and adverse events. .. = not reported. ANRS=Agence Nationale de Recherches sur le SIDA. AZT=zidovudine. BIPAI=Baylor International Pediatric AIDS initiative. DREAM=Drug Resources Enhancement against AIDS and Malnutrition. D4T=stadivudine. EFV=efavirenz. MTCT=mother-to-child transmission. NRTI=nucleoside reverse transciptase inhibitor. NNRTI=non-NRTI. NVP=nevirapine. PI=protease inhibitor. 3TC=lamivudine.

Characteristics of ART programs and children initiating ART

Information on treatment initiation and immunological or virological outcomes were available from 30 studies (table 1). 27 of 29 (one study did not provide this information [49]) studies reported a period of enrolment after 2000, and over half of the studies (65%) reported results on fewer than 200 children, with the largest consisting of multisite studies [17,44,45], or studies from large urban areas with 200–4062 children (table 1) [15,18,30,43,47,50,56,59,60]. All studies were done in urban centres, although one study reported a small proportion of children who had been treated in rural health centres [15]. Most studies were from treatment programmes that provided free antiretroviral therapy through government or donor organisations, and only two were established cohort studies of children who subsequently received antiretroviral therapy [9,19].

The children receiving antiretroviral therapy ranged from infants aged 2 months to adolescents aged 15 years, although children starting antiretroviral therapy were most often of school age (6 years). In the 26 studies that reported the age at which children started antiretroviral therapy, 19 studies (73%) reported a median or mean age of 5 years or older. Only two studies reported a median age below 2 years [30,45]. Some of the variation in age at antiretroviral therapy initiation may have resulted from differences in the age limits used to classify children, because the maximum paediatric age ranged from 12 years to 18 years. The proportion of boys receiving antiretroviral therapy ranged from 42% to 66% (table 1).

Most children were severely immunosuppressed and had advanced or severe disease before starting antiretroviral therapy, following WHO or US Centers for Disease Control and Prevention (CDC) treatment guidelines [80,81]. 19 studies reported a median percentage of CD4 T cells in children starting antiretroviral therapy of 6–15%, and ten (53%) studies reported a median of less than 10% (table 1). The proportion of children with less than 15% CD4 T cells, an indication of severe immunosuppression, ranged from 56% to 96% (table 1). 11 studies reported results of HIV viral load testing before starting antiretroviral therapy [9,18,24,30,31,42,49,51,56,62,65]. The mean or median HIV viral load reported in eight studies ranged from 5·0 to 6·1 $\log_{10}$ copies per mL [9,30,31,42,49,56,62,65]. Two studies reported that 164 (55%) of 297 children and 82 (82%) of 100 children had viral loads greater than 5·0 $\log_{10}$ copies per mL [18,24] and two studies reported that 111 (30%) of 367 children and 304 (39%) of 787 children had viral loads greater than 6·0 $\log_{10}$ copies per mL (table 1) [30,56].

Only two studies described how children were referred for antiretroviral therapy [13,31]. In Kenya, 69% of children were referred after hospital admission and the remainder from other outpatient clinics [31]. In Côte d'Ivoire, 64% were referred by the paediatric department or other health-care settings, 24% from the network of persons living with AIDS, and 12% from prevention of mother-to-child transmission (PMTCT) programmes [13].

Antiretroviral Therapy Regimens

24 of 30 studies described the antiretroviral regimens used (table 1). The most common regimen (92% of studies) included two nucleoside reverse-transcriptase inhibitors plus one non-nucleoside reverse-transcriptase inhibitor, typically a combination of zidovudine or stavudine, lamivudine, and efavirenz or nevirapine. Five studies (21%) reported using adult fixed-dose combinations of

stavudine, lamivudine, and nevirapine [17-19,31,49]. Fixed-dose combinations were used in an additional six studies that did not report immunological or virological treatment outcomes [27-29,67,70,74]. Didanosine and abacavir were used in nine studies (38%), but were primarily available as second-line drugs or for children receiving rifampicin. Protease inhibitors, including lopinavir-ritonavir, ritonavir, or nelfinavir, were used in 15 (63%) studies, primarily as first-line drugs for children under 3 years of age or as second-line drugs.

Reasons for the use of specific regimens were not reported, with the exception of adult fixed-dose combinations, which were used because alternative paediatric formulations were not available. These combinations were divided according to the child's weight and were not given to children weighing less than 10 kg.

Treatment outcomes

Clinical outcomes

The nutritional and clinical status of children improved in the 17 studies that examined these factors [13,15,16,18,19,23,30,31,37,48–50,53,55,60,65,66]. On average, children gained 1.8–3.6 kg in the first year of treatment [19,53,55,60,66]. In general, the mean or median weight-for-age Z scores were −2 or below at baseline and improved substantially by approximately 1 SD by 12 months of treatment [16,18,19,23,30,31,37,49,50]. These improvements were maintained 2–3 years after the start of antiretroviral therapy in studies of longer duration [13,65]. Mean or median height-for-age Z scores were also −2 or below at baseline and improved with treatment [13,15,16,23,30,31,37,49]; however, the gains were not significant in several studies [13,15,23]. In one study, the incidence of diarrhoea and pneumonia decreased by 64% and 56%, respectively [13], and in two studies, the frequency of hospital admissions decreased by 58% and 71% after treatment initiation [31,48].

Immunological outcomes

28 studies reported significant immunological reconstitution in children receiving antiretroviral therapy. CD4 T-cell percentage increased within the first year of treatment and then seemed to plateau after 12–18 months of treatment (figure 1). The median gain in percentage of CD4 T cells was 7.0–13.8% at 6–8 months [15,17,19,23,31,43,45,66], 10–16% at 12–15 months [16,17,23,31,42,50,52,60], 10% at 24 months [52], and 21% at 36 months [65]. Estimates of the percentage of CD4 T cells at least 1 year after the start of treatment were based on very few children. The proportion of children with less than 15% CD4 T cells during follow-up was reported from two studies, with the proportion decreasing from 56% and 66% at baseline to 8.8% and 10.7%, respectively, within 1 year of treatment [18,30].

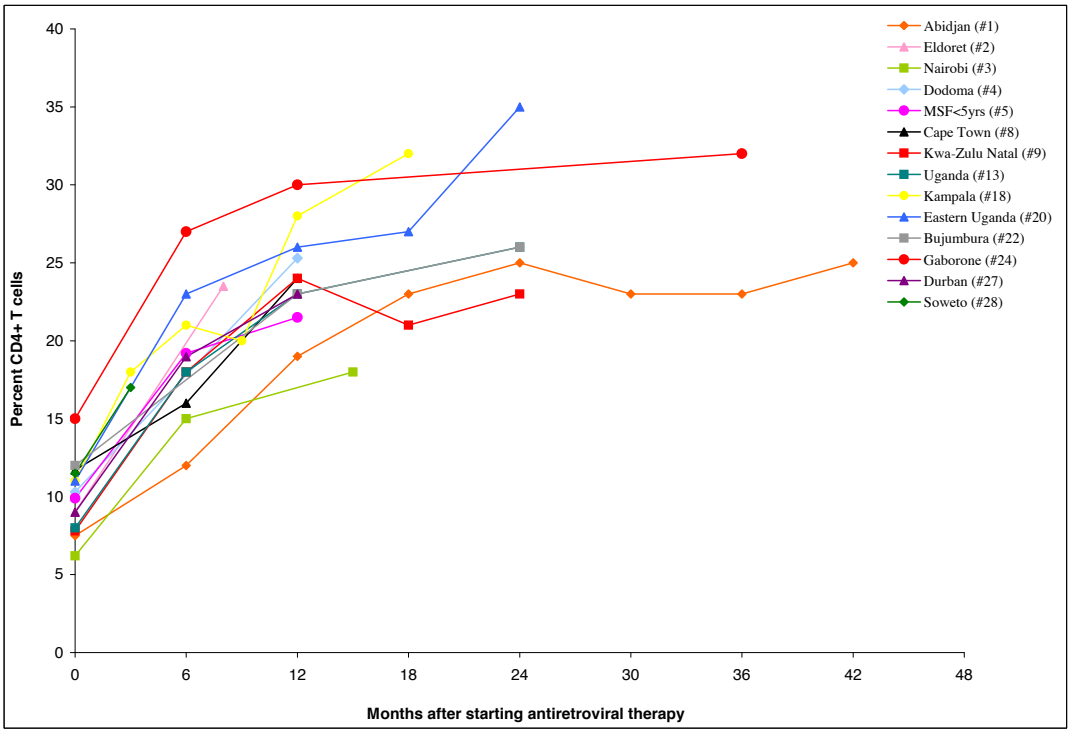

Figure 1: Immunological response among children receiving antiretroviral therapy in sub-Saharan Africa
28 studies reported on immunological outcomes but only 14 studies are shown here. The studies that are not represented here gave increases in CD4 T-cell % compared with baseline, the proportion less than 15% over time, or CD4 T-cell count over time. MSF=Médecins Sans Frontières.

Virological outcomes

All 17 studies with the capacity to measure HIV viral load reported significant declines after treatment initiation (figure 2) [9,13,18,20,23,24,30,31,42,44,47,49,51,52,54,56,57,60,64,65], with median viral load decreasing by approximately 2.0 $\log_{10}$ copies per mL within 1 year of starting therapy [9,31,42,49,57,60,64]. Viral load then remained stable for the duration of treatment, although this was based on data from only two studies [9,31].

Studies defined viral suppression differently depending on the lower limit of assay detection. For studies with a lower limit of detection of 250 copies per mL, 400 copies per mL, or unknown, the proportion of children achieving viral suppression was 54–55% at 3 months [31,64], 46–81% at 6 months [18,20,24,31,44,56], 68% at 9 months [31], and 49–81% at 12 months after starting therapy [13,30,42,44,47]. In four studies of longer duration, viral suppression was achieved in 50% of children at 24 months [9], 47–83% at 36 months [9,44,56,65], and 45% at 42 months [9].For studies using an assay with a lower limit of detection of 50 copies per mL, viral suppression was achieved in 64% and 84% of children at 6 months [23,51], 67–100% at 12 months [23,51,54], 72% at 18 months [23,51], and 67–93% at 24 months [23,51,54]. The reason for the higher rate of viral suppression in studies that used the more sensitive assay is not clear. In all studies measuring viral load and viral suppression, only a few children were followed for longer than 12 months.

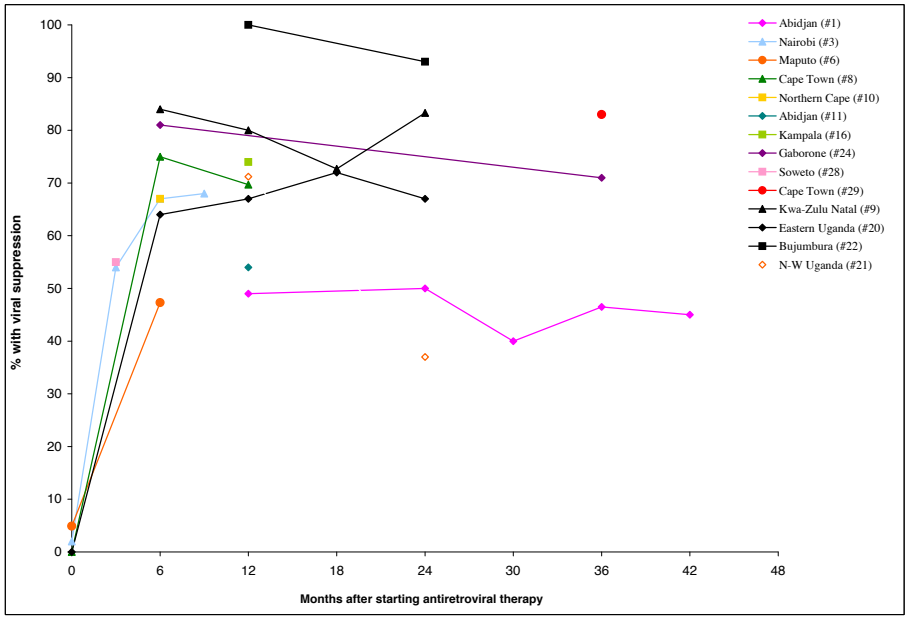

Figure 2: Percentage of children in sub-Saharan Africa achieving virological suppression after starting antiretroviral therapy

Triangles indicate undetectable level of <50 copies per mL; circles indicate undetectable level of <250 or <400 copies per mL or unknown; square indicates undetectable level of <1000 copies per mL. 17 studies reported on virological outcomes but only 14 studies are shown here. The studies that are not represented here reported on viral load over time (rather than viral suppression) or decreases in viral load over time. NW=north-western.

Genotypic drug resistance testing was done in four studies [10,42,52,79]. The proportion of children failing to achieve virological suppression with resistance to at least one class of drugs was 71–85% [10,52,79]. In two studies, among all treated children, the proportion with resistance to at least one class of drugs was 23% and 44% [10,42]. Resistance mutations to lamivudine or non-nucleoside reverse-transcriptase inhibitors were most common. In Côte d'Ivoire, 62% of children receiving regimens containing lamivudine and 78% receiving efavirenz-containing regimens had reverse-transcriptase mutations [10]. In children treated with nelfinavir-containing regimens, 38% had protease resistance mutations [10].

Adherence

Adherence was assessed in 12 studies by various methods, including caregiver recall, pill counts at scheduled visits, and unannounced pill counts at home (table 2) [11,15,20,23,25,27,31,33,50,67,69,71,72,76]. Compliance with scheduled visits was only reported in two studies and was 55% [71] and 88% [69]. However, the provision of more than 1 month's supply of drugs complicated this measure [71]. Adherence by caregiver recall was reported to be 29–82% for perfect adherence in the specified time period (3 or 7 days, or 1 month) [11,15,23,25,31,33,50,76], and 80–92% for those taking at least 95% of doses [23,27,69,72]. A mean adherence of 95% [67] and 97% [27] was reported in two studies.

Adherence by pill count or measured medications ranged from approximately 80% of children consuming more than 85% of pills [20] to an average of 93% and 99% of pills consumed [27,71]. Whereas adherence by pill count seemed to be high, in one study with a mean adherence of 93%, only 41% of children achieved more than 95% adherence [71]. In one comparative study, adherence was measured by three different methods: 72% achieved more than 95% adherence as assessed by unannounced pill counts, which was lower than by caregiver report (89%) or pill counts at scheduled clinic visits (94%) [27].

Reasons for missing doses of medication included the child forgetting, refusing, or vomiting without re-dosing [11,23,76], drug stock exhaustion[11,69,73,76], delays in getting new prescriptions because of financial constraints, long distances to travel, and long waiting times [11,23,25,69,73,76], incorrect dosing by caregiver [23], confusion between multiple caregivers [23,73], and problems of disclosure [25,73,76], particularly fear of disclosure because of HIV-related stigma [25,73]. In a qualitative study in Uganda, barriers also included the child's and caregiver's attitude towards antiretroviral therapy and the perceived benefits of the drugs; a supportive relationship with an adult, such as a family member, health-care provider, or teacher, was found to increase adherence [25].

Table 2: Adherence to antiretroviral therapy and visit compliance among HIV-infected children in sub-Saharan Africa.

	Location	Number of children	Self-reported adherence	Visit pill count	Unannounced pill count	Visit compliance
Published studies						
ANRS 1244 and 1278[11]	Abidjan, Cote d'Ivoire	112	67% perfect adherence	..	..	..
AMPATH clinics[15,33]	Eldoret, Kenya	279	75% perfect adherence	..	..	..
Kenyatta National Hospital[31]	Nairobi, Kenya	67	64% perfect adherence	..	..	..
The Mildmay Centre[25]	Kampala, Uganda	42	29% perfect adherence	..	..	..
Nabukeera et al[27,72]	Kampala, Uganda	170	Mean: 97%	Mean: 99% 94% >95% adherence	Mean: 94% 72% >95% adherence	..
Red Cross Children's Hospital[20]	Cape Town, South Africa	80	89% >95% adherence	80% >85% adherence	..	..
Reddi et al[23]	KwaZulu-Natal, South Africa	151	60% perfect adherence 89% >95% adherence	..	..	..
Abstracts						
Mukhtar Yola et al[69]	Kano, Nigeria	40	80% >95% adherence	..	..	88% kept all appointments
Tene et al[71]	Yaounde, Cameroon	108	92% appropriate adherence	Average: 93% 41% >95% adherence	..	55% satisfactory
Nalubega et al[67]	Kampala, Uganda	78	Mean: 95%	..		..
Semwendero et al[76]	Kampala, Uganda	117	72% perfect adherence	..		..
The Mildmay Centre[50]	Kampala, Uganda	355	82% perfect adherence	..		..

Risk factors for non-adherence included someone other than the mother administering antiretroviral therapy (grandparents in particular) [71,76], living outside an urban area [71], only the primary caregiver being aware of the child's HIV status [27], fewer hospital admissions before the start of antiretroviral therapy [27], no adult caretaker in the home also on antiretroviral therapy [67], receiving the lopinavir-ritonavir combination [76], and partial disclosure to the child (ie, the child being not fully aware of their status, but gaining information about their illness from sources other than their parents) [25]. Differing results were reported for the child's age as well as the duration on antiretroviral therapy [11,67,71,76].

Adverse events

The proportion of children experiencing adverse events associated with antiretroviral therapy varied from 2.5% in South Africa to 29% in Côte d'Ivoire, and is probably because of the different methods of classifying adverse events (table 3) [13,17,18,20,26,31,48,50,54,58,68]. Four of 11 studies reported that more than 20% of children had adverse events [13,18,31,58]. Most adverse events were mild, and the most common were gastrointestinal problems and skin rashes. Severe adverse events occurred in 0–10% of children [13,16,17,18,20,23,26,31,46,48,58,64,70,74,78], with five studies reporting percentages of 8–10% [13,16,31,64,78]. Serious adverse events resulted in either suspension of antiretroviral therapy or drug substitution.

Immune reconstitution disease

Few studies reported immune reconstitution disease in children (including one by Barry and colleagues [82] that was excluded from the previous review because only infants were enrolled) [22,39]. In 122 children in CapeTown, South Africa, three (2.5%) developed suppurative, regional lymphadenitis, and BCG site ulceration within 4 weeks of starting antiretroviral therapy, and all required antimycobacterial therapy [39]. In a separate case series [22], investigators described 11 cases of tuberculosis-associated immune reconstitution disease, four with new diagnoses of pulmonary tuberculosis, three with recurrent pulmonary tuberculosis after treatment for tuberculosis before antiretroviral therapy, and four with paradoxical reactions who were already receiving both antiretroviral therapy and antituberculous treatment. In 36 children younger than 1 year of age, immune reconstitution disease was documented in ten children (28%), with nine having BCG reaction, and one child with tuberculosis [82].

Regimen changes

Changes in drug regimens were not reported consistently, and distinctions between drug substitutions and regimen switches were not clear. Consequently, a change in at least one antiretroviral drug is reported here to best summarise reported results. A change in at least one antiretroviral drug was experienced by up to 59% of children [13,15,16,23,24,31,44,51,56,64]. Of the ten studies reporting changes in drug regimen, five reported that more than 15% of children changed drugs [13,16,31,51,56]. More than one change during the study period was rare. The main reasons for changing regimens were serious adverse events, treatment failure, and concomitant treatment of tuberculosis. The median time to a change ranged from 5 months to 17 months after antiretroviral therapy initiation [13,16,31,51,56].

Table 3: Adverse events reported among children receiving antiretroviral therapy in sub-Saharan Africa.

	Location	Number of children with adverse events	Number of children with serious adverse events	Reported adverse events
Published studies				
ANRS 1244 and 1278[13]	Abidjan, Cote d'Ivoire	23 of 78 (29%)	7 of 78 (9%)	Mild: diarrohea, increase in amylase, peripheral neuropathies, anaemia, vomiting, stomach pains, allergic symptoms (eg. dermatitis), conjunctivitis Severe: pancreatitis, persistent diarrhoea, anaemia, cutaneous allergy, increased liver enzyme activity
Diack et al[26]	Dakar, Senegal	4 of 36 (11%)	1 of 36 (3%)	Mild: vomiting, rash
Kenyatta National Hospital[31]	Nairobi, Kenya	>20%*	7 of 67 (10%)	Mild: rash, nausea/vomiting Severe: rash, anaemia, abacavir hypersensitivity
Ble et al[16]	Dodoma, Tanzania		6 of 59 (10%)	Severe: neutropenia, anaemia
Multisite Medecins Sans Frontiere project[17]	Cambodia, Kenya, Malawi, Mozambique, Thailand, Uganda, Burkina Faso, Zimbabwe	46 of 1184 (4%)	26 of 1184 (2%)	---
DREAM program[18]	Mozambique	>20%*	8 of 267 (3%)	Mild: liver toxicity, skin rash, anaemia Severe: liver toxicity, skin rash including Stevens- Johnson syndrome, anaemia
Red Cross Children's Hospital[20]	Cape Town, South Africa	2 of 80 (2.5%)	0	Mild: persistent nausea and vomiting, poorly tolerated taste
Reddi et al[23]	KwaZulu-Natal, South Africa		2 of 151 (1%)	Severe: anaemia, lactic acidosis
Abstracts				
Warren et al[46]	Addis Ababa, Ethiopia		0	---
Nannyonga Musoke et al[48]	Kampala, Uganda	4 of 83 (5%)	2 of 83 (2%)	Peripheral neuropathy, rash, hepatic toxicity
The Mildmay Centre[50]	Kampala, Uganda	28 of 355 (8%)		Nausea/vomiting, rash, neuropsychiatric disorders
Nabacwa et al[68]	Kampala, Uganda	>7%*		Rash, peripheral neuropathy, headache, diarrhoea
Kariyo et al[54]	Bujumbura, Burundi	>7%*		Anaemia, rash, lipidystrophy
DeNaeyer et al[70]	Kigali, Rwanda		>5.2%*	Severe: hepatic abnormalities and skin manifestations
Vaz et al[74]	Maputo, Mozambique		>1%*	Severe: Stevens-Johnson syndrome, peripheral neuropathies, lipoatrophy syndrome
Woldetsadik et al[58]	Botswana-Baylor Children's Clinical Centre for Excellence	23 of 110 (21%)	3 of 110 (3%)	Mild/moderate: Rash, severe anaemia, vomiting Severe: Stevens-Johnson syndrome
Feucht et al[78]	Pretoria, South Africa		23 of 259 (9%)	Mild: skin rashes, gastro-intestinal manifestations, neurological side effects
Moultrie and Meyers[64]	Soweto, South Africa		7 of 87 (8%)	---

Mortality and loss to follow-up

Mortality during follow-up was generally low (table 1): seven of nine studies with a duration of less than 1 year reported a mortality greater or equal to 5% (range 3–9%) [15,17,19,23,24,28,31,55,66], four of 14 studies of 1–2 years had a mortality greater than 10% (range 0–15·4%) [16,18,28–30,45,47,48,50,51,59,62,75,78], and one of three studies of 3 years reported a mortality greater than 10% (range 5·0–11·5%) [9,56,65]. The probability of survival 1 year after the start of

antiretroviral therapy was 84–97% [9,13,17,23,30,52,75].

A study from Côte d'Ivoire provided information on survival for over 3 years of follow-up, with 92.3% survival at 6 months, 91% at 12 months, 88% at 18–36 months, and 86% at 42 months after start of antiretroviral therapy [9,13]. Most deaths occurred within 6 months of treatment, with several studies reporting a mean or median time to death of 57–182 days [13,17,31,51,78], and others reporting that 55–100% of deaths occurred within the first 6 months of treatment [20,23,24,29,55]. Causes of death were reported in several studies; however, the methods of ascertaining or verifying causes of death were not disclosed and accuracy was uncertain [13,19,23,24,31,68]. The most commonly reported risk factor for death was a low CD4 T-cell percentage at the start of treatment [13,19,29,30,50,59,62]. Other risk factors included age less than 12–18 months [29,30], WHO stage 3 or 4 disease at treatment initiation [23,29,30,59], viral load greater than 6.0 $\log_{10}$ copies per mL [30], severe malnutrition [19,23,29], HIV-positive primary caregiver [23], and the presence of tuberculosis, gastroenteritis, pneumonia, or *Pneumocystis jirovecii* pneumonia at treatment initiation [23,55]. In Mozambique, investigators compared mortality among children receiving antiretroviral therapy and HIV-infected children ineligible for treatment, and found that mortality was higher (hazard ratio 3.8, 95% CI 1·9–7·5) for the untreated group, despite better immunological and virological conditions at baseline [18].

Loss to follow-up was low in most studies (table 1). Studies of less than 1 year reported losses to follow-up of 0–11% [15,17,23,28,55,66] and most reported that some children transferred to another treatment programme (0.1–7.3%) during that time [17,23,28,55,66]. Studies of 1–2 years reported losses of 1–9% [18,28–30,47,48,62,75], and transfers of 6.0–11·.% [28-30]. Studies of up to 3 years reported losses of 5.0–7.6% [9,56,65], and transfers of 15% [56].

Panel: Obstacles and strategies for improving treatment outcomes among HIV-infected children in sub-Saharan Africa.
Non-standard monitoring and assessment systems Develop guidelines for monitoring, assessment, and reporting to allow standardized data to be gathered and compared
Older age and advanced levels of immunosuppression at treatment start 1. Increase access to easy-to-use technologies for diagnosing HIV-1 infection in children 2. Earlier diagnosis of HIV-1 infection: strengthen voluntary testing and counseling programmes; and strengthen prevention of mother-to-child transmission programmes
High malnutrition at treatment initiation Develop integrated models of care: combine both therapeutic and supplementary feeding with treatment programmes
Suboptimal antiretroviral regimens available for use 1. Increase access to paediatric formulations 2. Develop paediatric fixed-dose combinations 3. Improve access to second-line drugs
Lack of reports from treatment programmes in rural areas 1. Support expansion of treatment programmes out of urban centers 2. Increase coverage in rural areas 3. Monitor and evaluate treatment programmes in rural areas

Discussion

We identified 30 studies that described the treatment of HIV-infected children in sub-Saharan Africa and that provided information on clinical, immunological, or virological outcomes. The early treatment outcomes reported in these studies are similar to those seen in observational studies in North America and Europe, despite greater obstacles to care and treatment. As with children in sub-Saharan Africa, treatment responses among HIV-infected children in North America and Europe vary, with 47–79% achieving virological suppression at 6 months [83-89], 53–75% at 12 months [83,85,87–89], 54–65% at 24 months [84,85,87,89], and 32–67% at 36 months [85,89]. In general, studies of treatment-naive patients in North America and Europe also reported decreases in HIV plasma viral load within the first 6 months of treatment in most children, and increases in CD4 T-cell percentage after the start of antiretroviral therapy [83,84]. However, the older age and greater disease severity at the time of treatment initiation in sub-Saharan Africa hinder direct comparisons with children in North America and Europe, and indicate that better outcomes could be achieved among these children.

Adherence in HIV-infected children in sub-Saharan Africa varied depending on the measurement used, but also were similar to those reported from high-income countries. In a recent review of antiretroviral therapy adherence in children residing primarily in North America and Europe [90], 100% adherence was reported by 34–100% of caregivers, mean adherence by pill count was 90%, and 100% of scheduled clinic visits were kept by 21–88% of children. Although it is hard to make meaningful comparisons, the studies from sub-Saharan Africa also reported results within these ranges. Loss to follow-up was also low in sub-Saharan Africa, with less than10% of children dropping out over the first 3 years of treatment. Additionally, loss to follow-up might have been overestimated in these studies, since many of those lost to follow-up may have died without their deaths being reported. Both of these concerns— difficulties with adherence and failure to remain in care—were raised during the scale-up of treatment programmes [5,6], because they could increase the risk of drug resistance, but have not been shown to be of greater magnitude among children in sub-Saharan Africa than in high-income countries.

Although it is encouraging that treatment programmes in sub-Saharan Africa are reporting responses similar to those from high-income countries, several issues emerge that are cause for concern and highlight areas in which improvements could be made to enhance successful treatment responses (panel).

First, the information reported from sub-Saharan Africa was not consistent across studies, making synthesis and summary of the data difficult. To adequately monitor and compare the progress of children starting antiretroviral therapy in different settings, standardised monitoring and assessment systems should be developed.

Second, children are entering treatment programmes at older ages in sub-Saharan Africa. Most children in these studies were older than 5 years when they started antiretroviral therapy. In a pooled analysis of mortality among HIV-infected treatment-naive African children, an estimated 35% and 53% died within 1 and 2 years, respectively [2]. By age 5 years, other studies have estimated that 62–89% of children have died [91-93]. Only a few studies reported on how children came to be

enrolled in the antiretroviral therapy programmes: most were identified as HIV-infected and clinically in need of treatment through health-care services, rather than in infancy through PMTCT or voluntary counselling and testing programmes, when children are often asymptomatic [13,31]. Therefore, older children with slower disease progression are more likely to gain access to antiretroviral therapy in sub-Saharan Africa. By contrast, nearly two-thirds of HIV-infected children who would have benefited from life-prolonging treatment before reaching age 5 years are not being diagnosed and treated.

Third, children in sub-Saharan Africa are entering treatment programmes with advanced immunosuppression. By definition, children eligible for treatment by CDC or WHO guidelines have moderate to severe immunosuppression [80,81]. However, with a median CD4 T-cell percentage of less than 10% in most studies, children in sub-Saharan Africa are starting antiretroviral therapy at more advanced stages of disease (CD4 T-cell percentage of approximately 5–10% lower) than children in high-income countries [83–86,88,89], thereby putting them at increased risk for treatment failure [85,94] and poor immunological response [84,89,94–96]. The late identification of clinically ill HIV-infected children at health-care facilities further supports the need for earlier diagnosis and treatment of HIV-infected children [7,97]. PMTCT programmes need to be strengthened to identify and monitor HIV-exposed children, and low-cost technology needs to be developed for the early diagnosis of HIV-infected infants. Earlier diagnosis will remain problematic if dependent on detection of HIV-1 DNA or RNA, although the use of dried blood spots will facilitate specimen collection, handling, and shipping [98]. Further development of less expensive but highly sensitive assays for the detection of p24 antigen on dried blood spots is thus needed [99]. Additionally, PMTCT programmes need to be linked with treatment programmes so that, once identified, infected infants can be treated. Criteria for starting antiretroviral therapy in children may also need to be revised so that children become eligible for antiretroviral therapy at less severe stages of disease progression and immune suppression. Preliminary results from the Children with HIV Early Antiretroviral Therapy study suggest that initiation of antiretroviral therapy before 12 weeks of age results in a 75% reduction in early mortality [100], and is likely to lead to efforts to revise treatment recommendations for children.

Fourth, more than half of the children reported were undernourished at treatment initiation [101]. Malnutrition is associated with disease progression and death in untreated children [102,103], and was associated with an increased risk of mortality among children receiving treatment in one study from South Africa [23]. In all studies that assessed this issue, nutritional status improved after antiretroviral therapy; however, the effect of malnutrition on virological success and immune reconstitution has not been fully explored. Treatment programmes need to address malnutrition and micronutrient deficiencies through an integrated model of care or by partnering with organisations that have the resources to provide nutritional supplementation [104]. One example of this approach is the Drug Resources Enhancement against AIDS and Malnutrition (DREAM) programme in Mozambique [18], which provides free HIV diagnosis and antiretroviral therapy in combination with nutritional assessment, food supplementation, treatment of tuberculosis and malaria, health education, and PMTCT. Micronutrient supplementation, such as with zinc [105], may also have the potential to reduce morbidity and mortality, particularly in children not yet eligible for antiretroviral therapy, although further research is needed.

Fifth, the available antiretroviral regimens for children are not ideal because palatable, stable liquid preparations, and fixed-dose combinations are not usually available for children, and second-line regimens are costly. Up to 59% of children required regimens to be changed because of treatment

failure or adverse reactions. From the limited number of studies that did resistance testing, most treatment failures were associated with the development of mutations that conferred resistance to an entire class of drugs. However, most studies only had nucleoside and non-nucleoside reverse-transcriptase inhibitors available in paediatric formulations, with only 63% of studies reporting the use of protease inhibitors. Additionally, five studies reported use of adult fixed-dose combinations as a pragmatic solution to the lack of paediatric formulations available in sub-Saharan Africa. However, a recent study in Malawi and Zambia reported that use of the fixed-dose combination of stavudine, lamivudine, and nevirapine resulted in subtherapeutic nevirapine concentrations in a substantial proportion of children if halved or quartered tablets were given.[106] This emphasises the need to increase access to paediatric drug formulations, avoid the use of adult fixed-dose combinations, and increase the availability of effective second-line drugs for children.

Finally, the studies reviewed reported results from treatment programmes implemented in urban centres. As programmes continue to expand from cities into surrounding communities, rural health centres will increasingly care for HIV-infected children. These children may differ in ways that could affect treatment outcomes, such as their clinical and immunological stage of disease at presentation, nutritional status, ability to access care (including distance, cost, and feasibility of travelling to the clinic), different patterns of comorbid conditions, and differences in stigma that could affect health-seeking behaviour and adherence. Additionally, rural clinics might face different logistical problems, including shortages of physicians and other clinic staff, making it more difficult to provide antiretroviral therapy and monitor patient progress and adherence. Several studies of adults and children have used a community-based model to provide antiretroviral therapy by integrating HIV services into primary health care in rural areas to overcome these obstacles, and have reported encouraging results [107,108]. The public-health community should continue to advocate increased access to care for HIV-infected children, particularly in rural populations, but it will be important to assess the effectiveness of these therapies as new challenges and obstacles are identified.

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Part Two: Barriers to care in rural Zambia

Chapter 3

Barriers to the care of HIV-infected children in rural Zambia: a cross-sectional analysis

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Abstract

Background: Successful antiretroviral treatment programs in rural sub-Saharan Africa may face different challenges than programs in urban areas. The objective of this study was to identify patient characteristics, barriers to care, and treatment responses of HIV-infected children seeking care in rural Zambia.

Methods: Cross-sectional analysis of HIV-infected children seeking care at Macha Hospital in rural southern Zambia. Information was collected from caretakers and medical records.

Results: 192 HIV-infected children were enrolled from September 2007 through September 2008, 28% of whom were receiving antiretroviral therapy (ART) at enrollment. The median age was 3.3 years for children not receiving ART (IQR: 1.8, 6.7) and 4.5 years for children receiving ART (IQR: 2.7, 8.6). 91% travelled more than one hour to the clinic and 26% travelled more than 5 hours. Most participants (73%) reported difficulties accessing the clinic, including insufficient money (60%), lack of transportation (54%) and roads in poor condition (32%). The 54 children who were receiving ART at study enrollment had been on ART a median of 8.6 months (IQR: 2.7, 19.5). The median percentage of CD4+ T cells was 12.4 (IQR: 9.2, 18.6) at the start of ART, and increased to 28.6 (IQR: 23.5, 36.1) at the initial study visit. However, the proportion of children who were underweight decreased only slightly, from 70% at initiation of ART to 61% at the initial study visit.

Conclusion: HIV-infected children in rural southern Zambia have long travel times to access care and may have poorer weight gain on ART than children in urban areas. Despite these barriers, these children had a substantial rise in CD4+ T cell counts in the first year of ART although longer follow-up may indicate these gains are not sustained.

Background

An estimated 2 million children under the age of 15 were living with HIV infection at the end of 2007, with almost 90% residing in sub-Saharan Africa [1]. Since the World Health Organization launched the '3 by 5' campaign in 2003 [2], dramatic improvements have been made to increase access to life-prolonging treatment for children in developing countries, with the number of children in sub- Saharan Africa receiving antiretroviral therapy increasing from approximately 50,000 in 2005 to over 150,000 by the end of 2007 [3].

Despite initial reservations about the implementation of antiretroviral treatment programs in Africa [4,5], recent reports demonstrate that treatment programs for HIV- infected children in sub-Saharan Africa can achieve outcomes similar to those in North America and Europe [6]. However, as the rollout of ART continues, concerns have been raised about how equitably access to ART has been distributed within countries [7-9]. HIV care services have primarily been implemented in urban areas and have lagged behind in rural areas, where there are shortages of trained personnel and the health care system faces many challenges [10]. Barriers faced by residents in rural areas may prevent them from accessing HIV care, including lower treatment literacy [11], greater distances and travel times to clinics [3], and fewer financial resources for transportation [12,13].

To address these issues, decentralized models for health care delivery have been developed to increase access to care in several rural settings [14-18]. Initial reports from rural programs have been promising [16-20]; however, further evaluation of rural HIV care programs is needed to understand the challenges to the care and treatment of HIV-infected persons, particularly children. We evaluated barriers to the care of HIV-infected children attending an HIV clinic in rural southern Zambia, with the goal of developing strategies to optimize the care of these children.

Methods

Study setting and population

HIV-infected children younger than 16 years and attending the Antiretroviral Clinic at Macha Hospital in Macha, Zambia were eligible for enrollment. Macha is located in Southern Province, approximately 80 km from the nearest town of Choma. The catchment area of Macha Hospital is populated by traditional villagers living in small, scattered homesteads, with an estimated population density of 25 persons per km^2 (P. Thuma, unpublished data). Macha Hospital is a 208-bed hospital administered by the Zambian Brethren in Christ Church that functions within the healthcare system of the Ministry of Health. The hospital serves as a district-level referral hospital for smaller hospitals and rural health centers within an 80 km radius, serving a population of over 150,000 persons. Macha Hospital provides care to approximately 4000 HIV- infected adults and children through the Government of Zambia's antiretroviral treatment program, with additional support from the President's Emergency Plan for AIDS Relief (PEPFAR) through the non-governmental organization, AidsRelief. A program to prevent maternal-to-child HIV transmission began at Macha Hospital simultaneous with the implementation of the ART clinic in 2005.

HIV-infected children are referred to the clinic from voluntary counseling and testing programs, outpatient clinics and hospitals. Since February 2008, children born to HIV- infected women are routinely tested for HIV infection at approximately 6 weeks of age, using dried blood spot samples

and HIV DNA PCR performed in Lusaka, Zambia. Clinical care is provided without charge by medical doctors and clinical officers, and adherence counseling by nurses and trained counselors. Home visits are attempted for persons who fail to return for scheduled follow-up visits. Children were considered eligible for antiretroviral therapy if they had WHO stage 3 or 4 disease, or a CD4+ T cell percentage of <25% for children < 11 months of age, < 20% for children 12-35 months of age, or <15% for children ≥ 36 months of age. The first-line antiretroviral treatment regimen consists of two nucleoside reverse transcriptase inhibitors (lamivudine plus zidovudine or stavudine) and a non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine).

Study procedures

This cross-sectional analysis was conducted within the context of an observational cohort study. HIV-infected children seeking outpatient care at Macha Mission Hospital, Choma, Zambia were prospectively enrolled into an observational cohort study beginning in September 2007 after written informed consent was obtained from a parent or guardian. The caretakers of all children who were asked to participate agreed to enroll in the study. A questionnaire developed by the study team was administered to the parent or guardian and the child was examined at the initial study visit and at each follow-up visit occurring approximately every three months. Blood specimens were collected in EDTA tubes as part of routine clinical care. Information from before study enrollment was abstracted from medical records. CD4+ T cell counts and percentages were measured using the Guava Easy CD4 system (Guava Technologies, Inc., Hayward, CA), and hemoglobin was measured using the ABX MICROS 60 (Hariba ABX, France). The study was approved by the Research Ethics Committee of the University of Zambia, the Ministry of Health, Republic of Zambia and the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health.

For the present analysis, information was used from the initial study visit for HIV-infected children enrolled into the cohort study between September 2007 and September 2008. Children were classified as HIV-infected if they were older than 18 months with a positive serological test, younger than 18 months with confirmed infection by PCR either prior to or within 3 months of the initial study visit, or younger than 18 months with a positive serological test and either eligible for ART based on the 2006 WHO treatment guidelines or receiving ART at the initial study visit.

Statistical Analysis

Data were entered in duplicate using EpiInfo (Centers for Disease Control and Prevention) and analyses were conducted in SAS for Windows version 9.1 (SAS Institute Inc., Cary, NC). Proportions are reported for categorical variables and differences were tested using chi-square tests. Medians and interquartile ranges are reported for continuous variables and differences were tested using Wilcoxon rank sum tests.

Children were categorized according to their use of ART at the time of the first study visit. Children who were not on ART were further categorized by eligibility for ART, as defined by the 2006 WHO treatment guidelines [21]. If laboratory results were not available at a specified clinic visit, results were used within a 3-month period (3 months prior for children initiating ART). Weight-for-age z-scores were calculated based on the WHO growth standards [22] and children with z-scores below -2 were defined as underweight. A measure of socio-economic status (SES) was calculated based on the Demographic and Health Survey SES scale used in Zambia [23]. SES percentiles were based on the predetermined cut-offs (<25th = 0-6; 26-50th = 7-12; 51-75th = 13-18; >75th = 19-24).

Results

Characteristics of study children

192 HIV-infected children were enrolled, 54 (28%) of whom were receiving ART at the initial study visit. These children represent approximately 70% of all HIV-infected children with at least one clinic visit between September 2007 and September 2008. The median age was 3.5 years (IQR: 1.9, 7.4; range: 0.3, 15.6) and 47% were boys (Table 1).

Table 1: Characteristics of HIV-infected children in the ART clinic in Macha, Zambia (2007 to 2008)

	Total (n = 192)	Not on ART (n = 138)	On ART (n = 54)
Child			
Median age in years (IQR)[a]	3.5 (1.9, 7.4)	3.3 (1.8, 6.7)	4.5 (2.7, 8.6)
Male (%)[a]	91 (47)	55 (40)	36 (67)
Parents			
Status (%)			
Both alive	121 (65)	94 (69)	27 (54)
Mother deceased	26 (14)	20 (15)	6 (12)
Father deceased	19 (10)	11 (8)	8 (16)
Both deceased	20 (11)	11 (8)	9 (18)
Primary Caregiver			
Relationship to child (%)			
Mother/father	139 (74)	104 (76)	35 (70)
Grandparent	28 (15)	17 (12)	11 (22)
Aunt/uncle	14 (7)	11 (8)	3 (6)
Sibling	3 (2)	2 (1)	1 (2)
Other	3 (2)	3 (2)	0 (0)
Median age (IQR)[b]	35.8 (30.3, 43.6)	35.5 (29.2, 43.6)	38.0 (33.3, 43.5)
Education (%)[b]			
None	8 (5)	5 (4)	3 (7)
Primary	98 (56)	75 (58)	23 (52)
Secondary	64 (37)	46 (35)	18 (41)
Higher	4 (2)	4 (3)	0 (0)
Household SES (%)			
≤25th percentile	131 (70)	97 (71)	34 (68)
26-50th percentile	48 (26)	33 (24)	15 (30)
51-75th percentile	7 (4)	6 (4)	1 (2)
76-100th percentile	1 (1)	1 (1)	0 (0)
Travel to ART clinic			
Median distance in km IQR)	28 (18-45)	28 (17-45)	30 (18-42)

ART = antiretroviral therapy; IQR = interquartile range; SES = socioeconomic status
[a]$p < 0.05$ for difference between HIV-infected children on ART and not yet on ART
[b]excluding respondents who are not the child's primary caregiver (n = 13)

The majority of children were cared for by a parent (74%), although 35% had lost one or both parents, and the majority of parents (96%) reported signs and symptoms of disease at the time of the initial clinic visit. Most children whose primary caregiver was not a parent were cared for by other family members, primarily a grandparent. The median age of the primary caregiver was 35.8 years (IQR: 30.3, 43.6) and their educational status was low, with 61% of caregivers achieving at most a primary level of education, and only 52% of these caregivers completed grade 7. The socioeconomic status of the households also was low, with 70% of children living below the 25th percentile. Children receiving ART at the initial study visit were older (median age: 4.5 vs. 3.3 years)

and were more likely to be male (67% vs. 40%), but were otherwise similar to children who were not receiving ART at the initial study visit. The use of antiretrovirals to prevent mother-to-child transmission in the study population was uncommon; seven children (4%), none of whom were receiving ART, received antiretrovirals in the perinatal period as confirmed by the medical record (n = 6) or self-report (n = 1).

Disclosure of HIV-infection status

As the study population was young, few children (3%) were reported to be aware of their HIV infection status. Among older children, only 5 (17%) of 29 children older than 10 years were aware of their status, with significantly more children receiving ART aware of their status (33% vs. 6%; P = 0.05). Of those children who were not informed of their HIV infection status, 83% were reported to be aware that they were sick (88% on ART vs. 81% not on ART; P = 0.70). Caregivers were asked to provide reasons for non-disclosure, and the primary reason (88%) was because they felt the child was too young to know. Forty-two percent of caregivers also reported that they had not disclosed the child's status because they were afraid to tell the child, 21% because they did not know how to tell the child, and 17% because they felt that it was not good for the child to know their HIV infection status.

Among all caregivers, 97% reported that someone other than themselves or the child was aware of the child's HIV infection status, with 47% reporting that only other family members had been told, 49% reporting that family members as well as others in the community (mostly neighbors) had been told, and 1% reporting that only other non-family members had been told. Significantly more caregivers of children on ART had disclosed to both family members and others in the community compared to children not receiving treatment (86% vs. 36%, $P < 0.0001$). Few caregivers (2%) reported being fearful of others finding out about their child's HIV infection status, or felt that they (3%) or their children (6%) were stigmatized because of their child's status. Significantly more caregivers of children on ART reported that they (9% vs. 1%, P = 0.004) or their child (16% vs. 2%, P = 0.0008) had been stigmatized. Among caregivers who reported feeling stigmatized, their children primarily experienced rejection by family (60%) and friends (50%), while the caregivers experienced rejection by their family (60%) and community (60%).

Clinic access

Children and their caregivers travelled an estimated median distance of 28 km (IQR: 18, 45) to attend the clinic. The majority of participants used a single mode of transportation, including walking (30%), cycling (39%) or public transportation (31%). The majority (91%) of participants travelled more than one hour to the clinic, with 26% travelling more than 5 hours (Figure 1). For participants who used motorized vehicles, 53% spent more than 20,000 ZMK (approximately 5 USD at that time) of their own (54%) or their family's (46%) money for transportation. No significant differences were found in mode, time or cost of transportation between children who were and were not receiving ART at study enrollment.

Seventy-three percent of participants reported ever experiencing problems accessing the clinic (Figure 2), primarily due to lack of money (60%), transportation (54%), and because roads were in poor condition (32%). No caretakers reported problems attending the clinic due to lack of time, forgetting about appointments or inability to find childcare. Caretakers tended to report more problems accessing the clinic during the rainy season (78%) from mid-November to mid-April than

during the dry season (67%, *P* = 0.2). Significantly more children not receiving ART reported problems attending the clinic than children receiving ART (79% vs. 59%, *P* = 0.01).

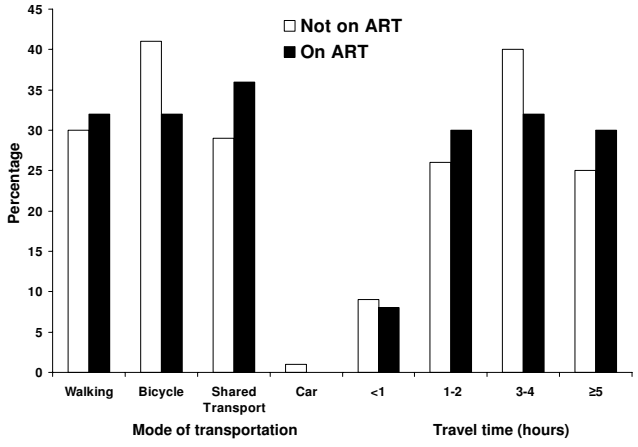

Figure 1: Method of transportation and travel time to the ART clinic among HIV-infected children.
Note: Modes of transportation are not mutually exclusive

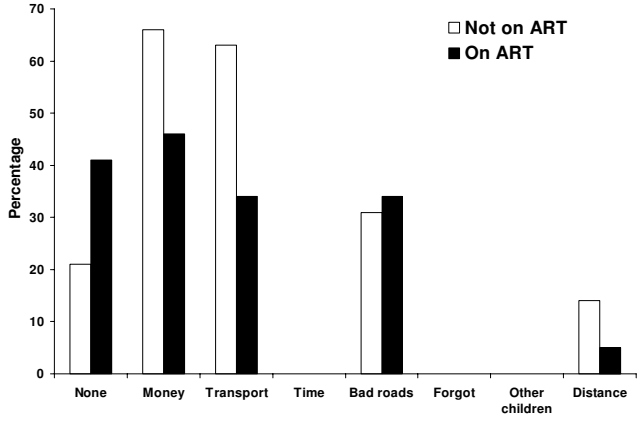

Figure 2: Problems experienced by HIV-infected children and their caregivers in travelling to the ART clinic in Macha, Zambia

Characteristics of children not receiving ART at the initial study visit

138 HIV-infected children were not receiving ART at study enrollment (Table 2). These children had been followed in the clinic a median of 3.2 months before study enrollment (IQR: 0.5, 10.1). The median percentage of CD4+ T cells was 20.7 (IQR: 16.0, 30.0), but 37% of children were severely immunosuppressed. In addition, 54% of children were classified as WHO stage 3 or 4 at the initial study visit. In this group, 79 (60%) children were eligible at the initial study visit to start treatment based on the 2006 WHO treatment guidelines [21]. These children had been followed in the clinic a median of 2.8 months (IQR: 0.4, 9.0), and for 14% of children this visit represented their first visit in the clinic. Children eligible for treatment were significantly younger (2.3 vs. 3.6), had lower median

WAZ (-2.4 vs. -2.1), and, as expected, had a lower median percentage of CD4+ T cells (17.4 vs. 29.6) and higher stage of disease progression (78% classified as WHO stage 3 or 4 vs. 0%). Based upon detailed review of the medical records of those children deemed eligible for ART at the initial study visit and who had been followed at the clinic a sufficient length of time to have a potential delay in initiation of ART, the most common reasons for a potential delay were loss to follow-up (10 children), concurrent tuberculosis (9 children) and need for adherence counselling (3 children).

Table 2: Characteristics at study enrollment of HIV-infected children not receiving ART

	Total (n = 138)	Children not eligible for ART[c] (n = 53)	Children eligible for ART at study enrollment (n = 79)
Median age (yrs) (IQR)[a]	3.3 (1.8, 6.7)	3.6 (2.5, 6.7)	2.3 (1.3, 6.7)
Male (%)	55 (40)	20 (38)	34 (43)
Length of time (months) since enrolling in ART clinic	3.2 (0.5, 10.1)	3.8 (0.2, 11.7)	2.8 (0.4, 9.0)
Median WAZ (IQR) (n = 120)[a,b]	-2.2 (-3.2, -1.3)	-2.1 (-2.7, -1.0)	-2.4 (-3.5,-1.6)
WAZ <-2	66 (55)	25 (53)	41 (59)
WAZ ≥-2	54 (45)	22 (47)	28 (41)
Median CD4+ T cell % (IQR) (n = 122)[a]	20.7 (16.0, 30.0)	29.6 (23.2, 36.9)	17.4 (12.1, 21.1)
Median CD4+ T cell count (IQR) (n = 126)[a]	815 (455, 1372)	980 (578, 1434)	735 (377, 1287)
Severe immunodeficiency[a,d]	47 (37)	0 (0.0)	47 (64)
Median total lymphocyte count (IQR) (n = 73)	4266 (2238, 7025)	3289 (2179, 4847)	4464 (2328, 7236)
Median hemoglobin (IQR) (n = 110)[a]	10.5 (9.2,11.6)	11.3 (9.8,11.7)	10.1 (8.8, 11.3)
Hemoglobin <8 gm/dL	6 (5)	1 (3)	5 (7)
Hemoglobin ≥8 gm/dL	104 (95)	36 (97)	68 (93)
WHO stage (n = 101)[a]			
1	17 (16)	11 (34)	5 (7)
2	33 (32)	21 (66)	10 (14)
3	38 (37)	0 (0)	38 (55)
4	16 (15)	0 (0)	16 (23)

ART = antiretroviral therapy; IQR = interquartile range; WAZ = weight-for-age Z score; WHO = World Health Organization
[a] $p < 0.05$ for difference between children eligible and ineligible for ART at study enrollment
[b] for children <10 yrs old
[c] eligibility for ART determined based on the 2006 WHO treatment guidelines; 6 children could not be classified as WHO stage and laboratory results were not available at baseline
[d] severe immunodeficiency defined by age according to WHO guidelines

Response to therapy among children receiving ART at the initial study visit

54 children were receiving ART at study enrollment (Table 3). These children had been followed in the clinic a median of 13.6 months (IQR: 6.4, 23.2) and had been on ART a median of 8.6 months (IQR: 2.7, 19.5). The median percentage of CD4+ T cells was 12.4 (IQR: 9.2, 18.6) at the start of ART and increased to 28.6 (IQR: 23.5, 36.1) at the initial study visit. The median increase in percentage of CD4+ T cells from ART initiation to the initial study visit was 18.1 (IQR: 6.0, 26.8). The percentage of CD4+ T cells increased with the duration of ART use (Figure 3). The proportion of children with a percentage of CD4+ T cells greater than 25% increased from 64% among those who had received ART for less than 12 months (n = 22) to 83% among those who had received ART for at least 12 months (n = 18). Children were not consistently classified according to WHO clinical stage; however, among those with WHO staging available (28 at ART initiation and 34 at the initial study visit) there was a decrease in the proportion of children in stage 3 or 4 from 89% at ART initiation to 65% at the initial study visit. However, the proportion of children who were underweight decreased only slightly, from 70% at ART initiation to 60.5% at the initial study visit for 37 children with available

data. WAZ scores increased a median of 0.24 (IQR: -0.57, 0.84) from initiation of ART to the initial study visit.

Table 3: Characteristics of children receiving ART (n = 54)

	At clinic enrollment	At ART initiation[a]	At study enrollment
Median age (yrs) (IQR)	3.6 (1.5, 7.7)	3.8 (2.0, 8.0)	4.5 (2.7, 8.6)
Median WAZ (IQR)[b]	-2.7 (-3.5, -1.5)	-2.5 (-3.9, -1.8)	-2.4 (-3.2, -1.5)
WAZ <-2	27 (61.4)	28 (70.0)	26 (60.5)
WAZ ≥-2	17 (38.6)	12 (30.0)	17 (39.5)
Median CD4⁺ T cell % (IQR)	14.0 (9.2, 19.0)	12.4 (9.2, 18.6)	28.6 (23.5, 36.1)
Median CD4⁺ T cell count (IQR)	505 (281, 985)	368 (219, 559)	973 (466, 1522)
Severe immunodeficiency[c]	16 (50)	24 (63)	2 (5)
Median total lymphocyte count (IQR)	3194 (1948, 5351)	2747 (1634, 5351)	3372 (1862, 5276)
Median hemoglobin (IQR)	10.6 (10.0, 11.7)	10.8 (10.0, 12.0)	11.9 (10.6, 12.3)
Hemoglobin <8 gm/dL	1 (2.0)	0 (0)	4 (8.9)
Hemoglobin ≥8 gm/dL	49 (98.0)	36 (100.0)	41 (91.1)
WHO stage			
1	2 (5.1)	2 (7.1)	6 (17.7)
2	9 (23.1)	1 (3.6)	6 (17.7)
3	22 (56.4)	20 (71.4)	20 (58.8)
4	6 (15.4)	5 (17.9)	2 (5.9)
ART regimen			
AZT/3TC/EFV	---	12 (26.1)	11 (42.3)
AZT/3TC/NVP	---	11 (23.9)	7 (26.9)
d4T/3TC/EFV	---	5 (10.8)	2 (7.7)
d4T/3TC/NVP	---	18 (39.1)	6 (23.1)

ART = antiretroviral therapy; IQR = interquartile range; WAZ = weight-for-age Z score; WHO = World Health Organization; AZT = zidovudine; 3TC = lamivudine; EFV = efavirenz; NVP = nevirapine; d4T = stavudine
[a]7 children transferred to Macha and had already initiated ART
[b]for children <10 yrs old
[c]severe immunodeficiency defined by age according to WHO guidelines

ART regimens and adherence

ART regimens at treatment initiation and the initial study visit consisted of a combination of 2 NRTIs and 1 NNRTI. Side effects were rarely reported, with only two children reporting a rash and one child reporting headaches after treatment initiation. A median of two adults (IQR: 2-3) were involved in supervising the administration of ART. The primary person responsible for ART administration was the child's mother (56%).

Sixty-one percent of children were living in households where at least one other person, primarily a parent, also was receiving ART. Among respondents, 22% of 41 reported problems with adherence. Among those who did, the primary reasons for a child missing a dose were forgetting (n = 2), the pills being either too numerous (n = 1) or too large to swallow (n = 1), the child refusing (n = 1), side effects (n = 2), the caregiver being away (n = 1), and finishing the supply of drugs prior to the next clinic appointment (n = 1).

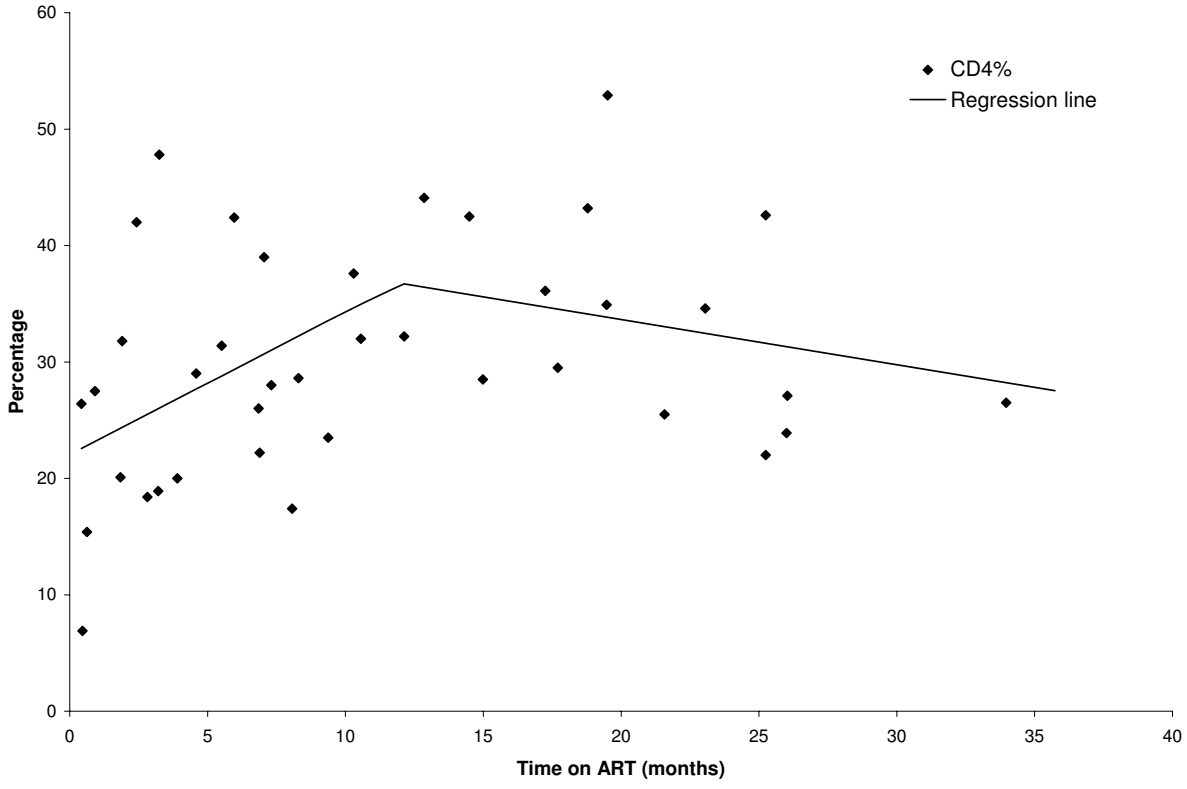

Figure 3: Percentage of CD4+ T cells after ART initiation for HIV infected children in Macha, Zambia

Discussion

Most assessments of the care of HIV-infected children in sub-Saharan Africa have been from urban sites, often from established research programs [6]. Our observations highlight barriers to the care of HIV-infected children unique to rural settings, specifically long travel times and lack of transportation, but are encouraging in that age at clinic enrollment and immunologic outcomes in the first year of treatment did not differ substantially from published reports on the care of HIV-infected children in urban sub-Saharan Africa. These findings suggest that the barriers to the care of HIV-infected children in rural settings do not pose insurmountable obstacles to desirable treatment outcomes.

The median age of HIV-infected children receiving care in rural southern Zambia was younger than commonly reported (4.5 years for children receiving ART and 3.3 years for children not receiving ART). Among studies reporting the effectiveness of pediatric ART in sub-Saharan Africa, 73% of 26 studies reported a median or mean age of five years or older at initiation of ART [6]. In Lusaka, Zambia, the median age at which HIV-infected children began care was 5.4 years (IQR: 1.9, 9.5) [24]. Thus, compared to this urban Zambian pediatric cohort, children accessing care in this rural setting do not appear to face additional delays; however, the number of children undiagnosed or not accessing care is not known. There is urgent need to diagnose HIV infection and initiate ART within the first year of life given the high mortality rate in early childhood [25] and the demonstrated benefits of initiating treatment in early infancy [26]. In rural Zambia, as elsewhere in sub-Saharan Africa, children accessing care are a subset of HIV-infected children with slower disease progression.

At Macha Hospital, infant diagnosis of HIV infection using dried blood spots and PCR was introduced in February 2008, and is likely to reduce the age at which HIV-infected children enter care.

One of the major barriers to care in rural sub-Saharan Africa is access to health facilities. In rural southern Zambia, more than 90% of HIV-infected children travelled more than one hour to the clinic and more than one quarter travelled more than five hours. Lack of transportation, insufficient financial resources and poor roads were commonly cited obstacles to accessing the clinic, particularly during the rainy season. Such obstacles are unlikely to be major barriers to care in urban settings and could result in suboptimal treatment outcomes for HIV-infected children residing in rural areas. Significantly more children not on ART reported problems accessing the clinic but the reasons are unknown. It may be that caregivers who have committed to providing ART for their child perceive fewer problems, as the journey to and from the clinic has become routine.

The majority of children (78%) were not receiving ART at the time of study entry. Although these children were followed for only a median of 3.2 months, some were deemed eligible for ART at study entry. Over a third were severely immunosuppressed and slightly more than half were classified as WHO stage 3 or 4 at the initial study visit. Consequently, many of these children were eligible for ART at the study visit according to the WHO guidelines. However, many met criteria for WHO stage 3 because of poor nutritional status, which in this setting does not necessarily represent advanced HIV disease and is not in itself a criterion for treatment initiation. In addition, many children had not been followed in the clinic long enough to fulfil the requirements for treatment initiation, including eligibility and adherence visits. For children who had been in the clinic a sufficient time, delayed initiation of ART could have resulted from biomedical, social or health care-associated factors. In a study conducted in Pretoria, South Africa, reasons for delayed initiation of ART among 147 eligible, HIV-infected children included: tuberculosis co-infection (26%); inadequate clinic staffing (20%); social problems, including lack of transportation, absence of legal guardian and denial (17%); and inaccurate clinical or immunological staging (14%) [27]. In this study, delays in initiation of ART most frequently resulted from loss to follow-up or concurrent tuberculosis. Given the advanced clinical and immunological stages at which children entered the clinic, delays in ART initiation could be detrimental, leading to higher pre-ART mortality [28], more rapid disease progression [26], or poorer response to treatment.

In rural Zambia, three quarters of the HIV-infected children seeking care had a parent as the primary caregiver, although one third had lost at least one parent. Children who are orphans [29] and children whose primary caregiver is not a parent [30] may be at increased risk for non-adherence to the antiretroviral regimen. Few children, even among the older age groups, were reported to be aware of their HIV-infection status, primarily because the caregivers thought the child too young to be told the diagnosis or they were afraid to tell the child. However, this finding must be interpreted with caution as this information was reported by the caregiver rather than the child and may be an underestimate of the children's true knowledge of their status.

Despite these barriers, the 54 children receiving ART at study entry achieved good immunological responses, with the percentage of CD4+ T cells increasing a median of 17.6% after a median of 8.1 months of therapy. This compares favorably with 28 published studies of the immunological response to ART among HIV-infected children in sub-Saharan Africa residing largely in urban settings,

in which the median gain in percentage of CD4+ T cells was 7-14% at 6-8 months and 10-16% at 12-15 months of therapy [6]. In contrast, weight gain among HIV-infected children receiving ART in rural Zambia did not achieve the levels reported elsewhere in sub-Saharan Africa, with WAZ scores increasing a median of 0.24 after receiving ART a median of 8.6 months. Among 17 published studies that reported nutritional outcomes, weight-for-age Z scores improved by 1 SD after twelve months of ART [6]. Similarly, among 749 HIV-infected Ugandan children who received ART for a mean of 6 months, the mean weight-for-age Z score increased from -3.2 to -2.1 over the study period [31]. HIV-infected children receiving ART in rural sub-Saharan Africa may have poorer weight gain because of lower dietary intake than children residing in urban areas.

Conclusion

HIV-infected children in rural southern Zambia have long travel times to access care and may have poorer weight gain on ART than children in urban areas. Despite these barriers, children in rural Zambia had a substantial rise in CD4+ T cell counts in the first year of ART although longer follow-up may indicate these gains are not sustained. Developing strategies to improve access to care and nutrition will be necessary to ensure optimal, long-term treatment outcomes for HIV-infected children residing in rural sub-Saharan Africa.

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Chapter 4

Differences in presentation, treatment initiation, and response among children infected with human immunodeficiency virus in urban and rural Zambia.

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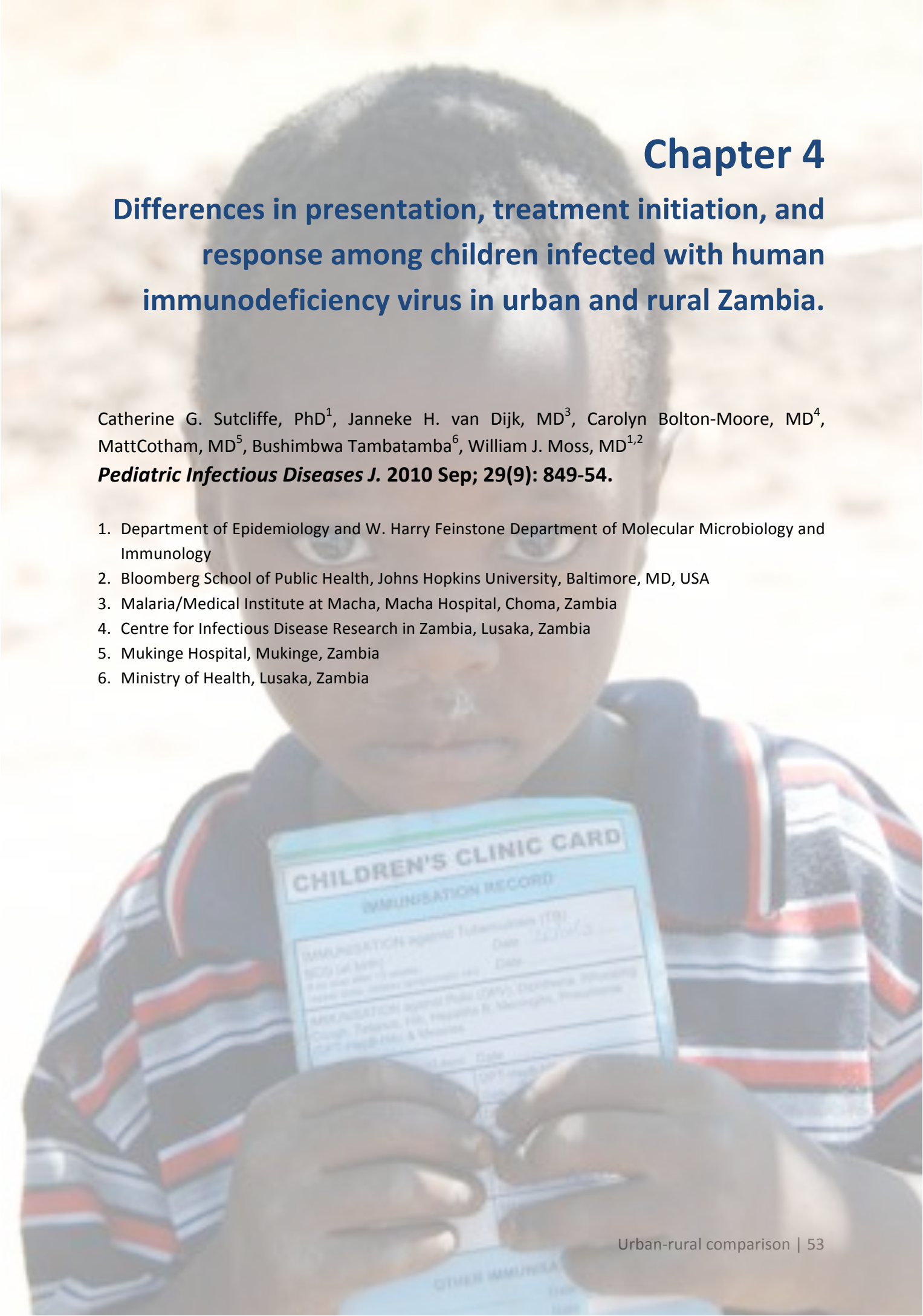

Abstract

Background: Access to pediatric antiretroviral therapy (ART) in rural areas remains limited due to the unique challenges faced by providers and patients. Few rural ART programs have been evaluated to determine whether these challenges affect care and treatment response**.**

Methods: Routinely collected data from 3 pediatric ART programs in rural and urban Zambia were obtained from medical records. Participants included human immunodeficiency virus-infected children <15 years of age presenting for care between August 2004 and July 2008. Characteristics at presentation, time to ART initiation, and treatment response were compared between urban and rural children.

Results: A total of 863 children were enrolled (562 urban and 301 rural). At presentation, children in rural clinics were significantly younger (3.4 vs. 6.5 years), had higher CD4 T-cell percentages (18.0% vs. 12.8%), less advanced disease (47.5% vs. 62.3% in World Health Organization stage 3/4), lower weight-for-age Z-scores (-2.8 vs. -2.3), and traveled greater distances (29 vs. 2 km). Rural children eligible for ART at presentation took longer to initiate treatment (3.6 vs. 0.9 months); no differences were found in time to ART initiation among children ineligible at presentation (15.4 vs. 12.1 months). For the 607 children initiating ART, clinical and immunologic status improved in both urban and rural clinics. Mortality was highest in the first 90 days of treatment and was higher at all times in rural clinics.

Conclusions: The findings support expansion of ART programs into rural areas to increase access to treatment services and reduce inequities.

Introduction

Despite progress in scaling-up pediatric antiretroviral therapy (ART) programs in sub-Saharan Africa [1], concerns have been raised about inequities in the distribution of ART [2,3]. Many human immunodeficiency virus (HIV)-infected children live in rural areas where access to therapy has been limited. Treatment programs in rural health facilities may face additional challenges, including inadequate infrastructure and shortages of trained health personnel [4-6]. Children and their caregivers residing in rural areas may face unique barriers to care, including greater distances to travel, greater direct and indirect costs, and limited knowledge of HIV/ AIDS testing and treatment services [2,5,7-9]. These factors can affect decisions regarding when to access HIV-treatment programs, the quality of care once enrolled, and ultimately treatment response.

Many pediatric treatment programs in urban settings in sub-Saharan Africa have treatment outcomes comparable to those observed in high-income countries [10], but data are limited from rural programs [11-16]. Few studies have focused on rural children [17] or directly compared urban and rural populations [18,19]. To address these issues, we sought to determine whether differences existed between HIV-infected children attending 1 urban and 2 rural HIV clinics in Zambia in terms of characteristics at presentation, time to ART initiation, and treatment responses.

Methods

Study Population

The study was conducted in 3 pediatric HIV clinics in Zambia. The urban clinic, Matero Reference HIV Clinic, is located in a low-income community in Lusaka and is 1 of 18 Ministry of Health facilities in the city supported by the Centre for Infectious Disease Research in Zambia that has provided care to HIV- infected children since May 2004 [20].

The 2 rural clinics were Macha Mission Hospital and Mukinge Hospital, which began administering ART in March 2005. Macha Mission Hospital, located in Southern Province, is a district-level hospital administered by the Brethren in Christ Church [17]. Mukinge Hospital, located in North Western Province, is a district-level hospital administered by the Evangelical Church in Zambia. Both areas have lower population density than Lusaka (63.5, 14.2, and 4.6 per km^2 in Lusaka, Southern Province and North Western Province, respectively) and are populated primarily by subsistence farmers [21].

The study was approved by the University of Zambia Research Ethics Committee, the Ministry of Health of Zambia, and the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

Clinic Procedures

Children referred with a documented positive serologic test underwent an initial clinical evaluation. Standard of care included measurement of $CD4^+$ T-cell counts/percentages (not available the first year in the rural clinics) and hemoglobin levels. Capacity to measure viral load was not routinely available.

ART eligibility was determined according to World Health Organization (WHO) [22,23] and national treatment guidelines [24]. DNA-based diagnostic testing became widely available in 2008; therefore, infection could not be confirmed in infants younger than 18 months during the study. Infants with

severe disease or immunodeficiency were presumptively treated [23].

The clinics followed similar visit schedules [15,20]. Eligible children were started on standard ART regimens (stavudine/zidovudine/abacavir plus lamivudine plus efavirenz/nevirapine) [24] after achieving adequate adherence with cotrimoxazole and multivitamins. Children were seen in the clinic up to 4 times during the first month of treatment, monthly up to 6 months, and then every 2 to 3 months, depending on progress and adherence. At each visit, children were seen by a clinical officer or medical doctor and received adherence counseling. Immunologic status was assessed every 6 months or when clinically indicated. Children ineligible for treatment were seen every 3 months.

Attempts were made to contact children who missed appointments. Deaths were reported by clinic reports or family members and approximate date and cause of death were ascertained. Children who could not be found or who had moved were deemed inactive (defaulted).

Statistical Methods

Data from the rural clinics were obtained from their electronic medical records system (CAREWare) and data from Matero Reference Clinic were abstracted from medical records (95% of files were located). HIV-infected children younger than 15 years with at least one clinic visit between implementation and July 31, 2008 were included in the analysis. Infants who were not presumptively diagnosed and treated and children transferring to the clinics already receiving ART were excluded.

Children were included in the analysis until they transferred to another clinic, died, defaulted, or were censored on July 31, 2008. Children who missed at least 2 clinic visits scheduled 3 months apart by the end of follow-up were censored at their last clinic visit (defaulted).

Eligibility for ART at the initial evaluation visit was defined retrospectively based on treatment guidelines in effect at that time. The 2003 guidelines relied more heavily on clinical judgment, consequently children with ambiguous or missing information were considered eligible if they started ART within 90 days of their initial evaluation. For all measures, results within 90 days were used if none were available at initial evaluation.

Nutritional status was defined using WHO growth standards [25]. Weight-for-age (WAZ), height-for-age, and weight-for-height z-scores below -2 were considered to be indicative of underweight, stunting, and wasting, respectively.

Distance to the clinic was self-reported in Macha and Mukinge. In Matero Reference Clinic, participants reported township of residence; geographic information system mapping was used to estimate the distance from the township center to Matero Reference Clinic. Children were classified as living a short, medium, and long distance from the clinic according to township for Matero (short: Matero; medium: adjacent to Matero; long: other/ outside Lusaka) and tertiles of distance for Macha (0 –23, 23.1– 40, >40 km) and Mukinge (0–7, 7.1–40, >40 km).

Time to ART initiation and survival post-ART initiation were assessed using Kaplan-Meier curves, with differences determined using log-rank tests. Overall mortality rates, as well as pre- and post-90 days of treatment, were calculated. Factors associated with each outcome were assessed using Cox proportional hazards models, with final models including location (rural vs. urban) and covariates found to be ($P < 0.05$) or known to be associated with the outcome.

Treatment outcomes were assessed immunologically, with $CD4^+$ T-cell percentage, and clinically, with WAZ. For both outcomes, children were included if they had a pre-ART measure and at least one post-ART measure. For reporting outcomes at specific intervals, measurements were aggregated to within 45 days. Treatment outcomes were evaluated using linear mixed effects models with

random intercept, exchangeable correlation structure, and robust standard error estimation. For both outcomes, models included terms for location, time, an interaction between location and time, and other covariates found to be (P <0.05) or known to be associated with the outcomes. For $CD4^+$ T-cell percentage, a spline term was added at 7.5 months, the upper window around the 6-month measure.

Analyses were conducted separately by rural site; as no major differences in outcomes were found, combined results are reported. Many children were missing information on clinical and immunologic measures; therefore, indicator variables for missing data were included in the models. Multiple imputation methods were also explored with no significant difference in the results.

Analyses were conducted using SAS for Windows, version 9.1 (SAS Institute Inc, Cary, North Carolina) and STATA, version 9 (StataCorp LP, College Station, TX).

Results

Between program implementation and July 2008, 863 treatment-naive children were enrolled (Fig. 1). Urban and rural children contributed a median of 11.9 months (Interquartile range (IQR): 2.8, 28.2; range: 0–46.4) and 9.9 months (IQR: 2.8, 19.7; range: 0–40.9) of follow-up, respectively (P <0.005).

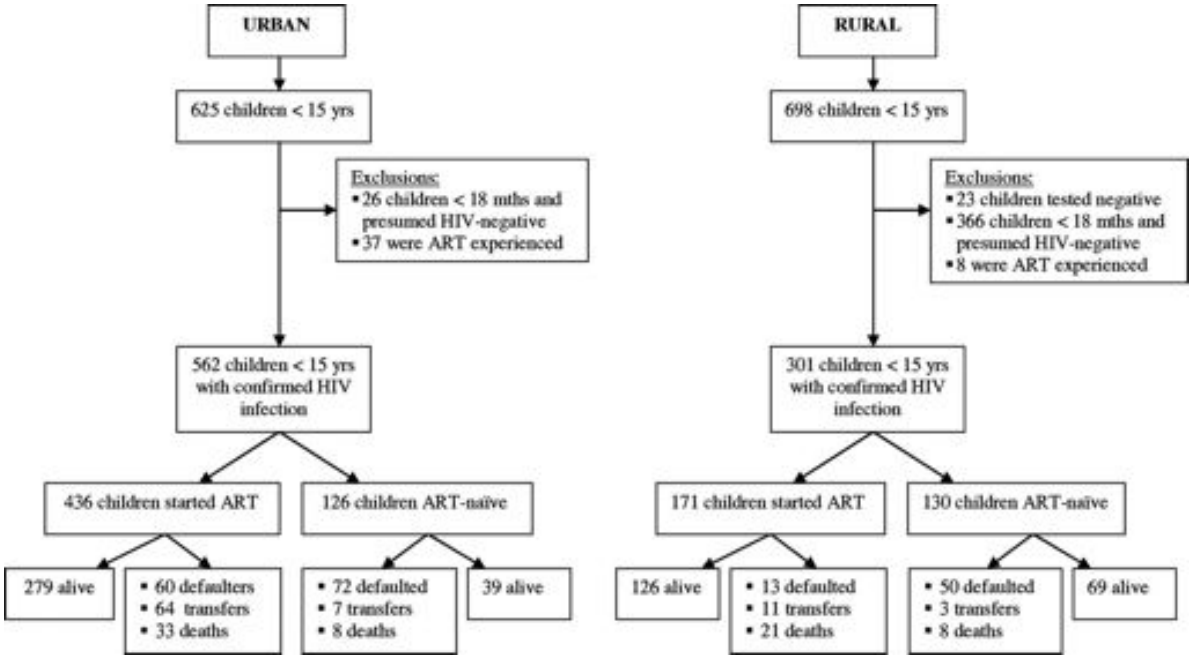

Figure 1. Children evaluated at 3 HIV clinics in urban and rural Zambia, August 2004 – July 2008.

Differences in Characteristics at Initial Evaluation

Significant differences were observed in the characteristics of urban and rural children at initial presentation (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A516). Urban children presented at an older age, were less likely to be underweight, and were more likely to report a history of tuberculosis, present with advanced disease and be eligible for ART. Urban children traveled shorter distances (median: 2.0 km; IQR: 1.4, 2.7) than rural children (median: 29.0 km; IQR: 12.0, 48.0).

Differences in Time to Initiation of Antiretroviral Treatment

Children Eligible for Treatment at Initial Evaluation

At the initial evaluation visit, 611 children were eligible for ART. By July 31, 2008, 82% had initiated ART, 6% were alive but were not on ART, and, prior to initiating ART, 1% died, 0.3% transferred to another clinic, and 11% defaulted. A higher proportion of rural children defaulted (15% vs. 10%; *P*= 0.10), or were alive and not on ART (12% vs. 4%; *P*<0.0001) than urban children.

Table 1. Factors associated with treatment initiation among HIV-infected children who were eligible and ineligible for treatment at their initial evaluation visit in urban and rural Zambia.

Characteristics of the child at the initial evaluation visit	Children eligible for ART (n=611)		Children ineligible for ART (n=224)	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Rural clinic	**0.40 (0.32, 0.50)**	**0.38 (0.29, 0.48)**	0.96 (0.64, 1.44)	**0.59 (0.37, 0.95)**
Age (yrs)				
< 2	0.92 (0.73, 1.15)		**2.33 (1.47, 3.69)**	**2.62 (1.57, 4.38)**
2-4.9	0.95 (0.76, 1.18)		0.84 (0.49, 1.44)	0.94 (0.53, 1.69)
≥ 5	1		1	1
Male sex	1.05 (0.88, 1.25)		1.09 (0.73, 1.63)	
History of tuberculosis	1.18 (0.97, 1.42)		1.63 (0.87, 3.06)	
Weight-for-age z-score				
< -3	1.12 (0.88, 1.42)		**3.23 (1.79, 5.82)**	**3.25 (1.77, 5.98)**
-3 to -2.1	1.15 (0.87, 1.51)		**2.03 (1.14, 3.62)**	**2.22 (1.21, 4.07)**
≥ -2	1		1	1
High WHO stage[a]	0.89 (0.73, 1.09)		1.31 (0.80, 2.13)	
Low CD4 %[b]	**1.88 (1.52, 2.34)**	**1.89 (1.52, 2.35)**	**2.12 (1.23, 3.66)**	**2.03 (1.17, 3.53)**
Hemoglobin < 8 g/dL	1.19 (0.93, 1.51)		0.93 (0.65, 1.32)	
Distance to the clinic				
Near	1		1	
Mid distance	1.02 (0.83, 1.26)		0.96 (0.58, 1.58)	
Far	0.89 (0.70, 1.13)		1.20 (0.71, 2.04)	

[a]For children eligible for ART, a high WHO stage was defined as WHO stage 3 or 4; for children ineligible for ART a high WHO stage was defined as WHO stage 2.

[b]For children eligible for ART, a low $CD4^+$ T-cell percentage was defined as CD4%< 15%; for children ineligible for ART a low $CD4^+$ T-cell percentage was defined as CD4% <25%.

Distance traveled was significantly associated with defaulting, with more children defaulting at greater distances (short: 6.8% vs. medium: 12.2% vs. long: 14.8%; *P*= 0.05, *P* for trend = 0.02), particularly in the rural areas (9.3% vs. 17.1% vs. 20.0%).

The time to ART initiation was significantly shorter for urban (median: 0.9 months; IQR: 0.5, 1.5) compared with rural children (median: 3.6 months; IQR: 1.0, 9.2; *P*<0.0001) (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/A517). Factors associated with ART initiation included low $CD4^+$ T-cell percentage and location (Table 1). Attending a rural clinic remained inversely associated with ART initiation even after adjusting for low $CD4^+$ T-cell percentage.

Children Ineligible for Treatment at Initial Evaluation

At the initial evaluation visit, 224 children were ineligible for ART. By the end of July 2008, 43% had initiated ART, 29% were still alive but not on ART, 3% died without initiating ART, 4% transferred to another clinic, and 21% defaulted, with no significant differences by location. The proportion of children defaulting was higher among ineligible children compared with eligible children (21% vs. 11%; *P* = 0.0001). Distance traveled was associated with the probability of defaulting (short: 14% vs. medium: 27% vs. long: 26%; *P* = 0.13, *P* for trend = 0.10), particularly among rural children (10% vs. 21% vs. 28%); however, this finding was not statistically significant.

The time to initiate ART after entering the clinic did not differ between urban (median: 12.1 months; IQR: 4.9, 30.9) and rural (median: 15.4 months; IQR: 6.1, 27.8; *P* = 0.84) children (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/A518). Factors positively associated with ART initiation included a low $CD4^+$ T-cell percentage, younger age, and lower WAZ (Table 1). After adjusting for these factors, attending a rural clinic was significantly inversely associated with ART initiation.

Differences in Antiretroviral Treatment Responses in Urban and Rural Clinics

By July 31, 2008, 607 children had initiated ART, contributing a median of 13.7 months (IQR: 3.8, 29.3) of follow-up on ART in the urban clinic and 7.6 months (IQR: 2.9, 16.3) in the rural clinics (*P*< 0.0001). Similar differences in the characteristics of urban and rural children were observed at ART initiation as were observed at initial evaluation (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A516).

$CD4^+$ T-Cell Response

Both urban and rural children showed significant improvements in $CD4^+$ T-cell percentages, particularly in the first 6 months of treatment (Fig. 2). Median increases in $CD4^+$ T-cell percentages after 6, 12, and 18 months of treatment were 11.3 (IQR: 6.6, 16.7), 14.4 (9.5, 21.0), and 16.7 (10.5, 22.8), respectively, with no differences by location.

In a longitudinal model (Table 2), urban children initiated ART with a lower $CD4^+$ T-cell percentage, but experienced the same pattern of immune reconstitution, resulting in consistently lower mean $CD4^+$ T-cell percentages throughout follow-up. Consequently, the proportion of rural children achieving a $CD4^+$ T-cell percentage of ≥25% was higher after 6 (58% vs. 42%), 12 (69% vs. 58%), and 18 months (86% vs. 68%) of treatment, although these differences were not statistically significant. Adjusting for age, sex and WAZ at ART initiation, differences by location were no longer significant.

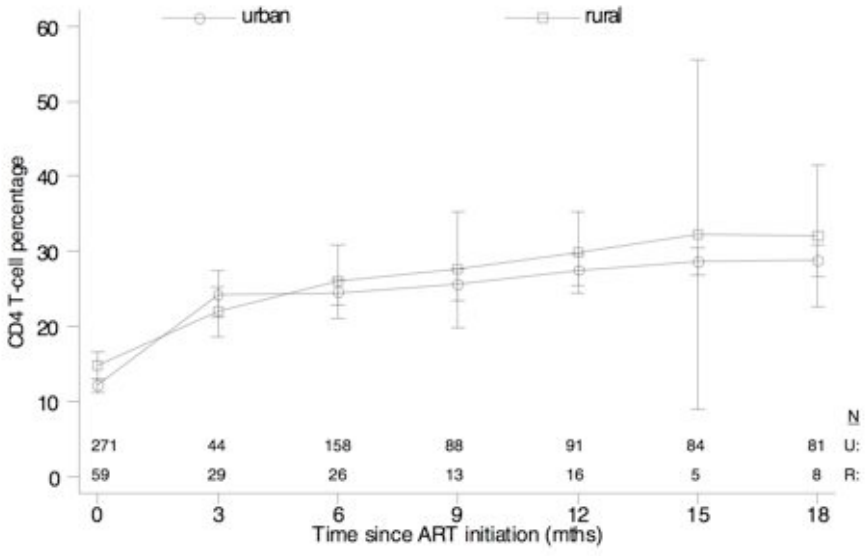

Figure 2. Mean (95% CI) CD4$^+$ T-cell percentage after treatment initiation among HIV-infected children in rural and urban Zambia.

Table 2. Change in weight-for-age z-scores and CD4$^+$ T-cell percentages after treatment initiation among HIV-infected children in rural and urban Zambia

	Crude			Adjusted		
	Urban	**Rural**	**p-value**	**Urban**	**Rural**	**p-value**
CD4$^+$ T–cell percentage[a]						
CD4 % at ART initiation (SE)	12.51 (0.49)	15.50 (1.17)	0.02	14.77 (1.47)	17.38 (1.80)	0.08
Increase per month in first 6 months (SE)	1.94 (0.06)	1.83 (0.23)	0.64	2.06 (0.08)	1.86 (0.21)	0.39
Increase per month after 6 months (SE)	0.13 (0.02)	-0.06 (0.18)	0.29	0.14 (0.03)	0.008 (0.16)	0.41
Weight-for-age z-score[b]						
WAZ at ART initiation (SE)	-2.26 (0.08)	-2.76 (0.11)	<0.0001	-2.30 (0.21)	-2.69 (0.24)	0.02
Increase per month (SE)	0.032 (0.0025)	0.056 (0.0057)	<0.0001	0.028 (0.0027)	0.055 (0.0089)	0.004

[a]Results from longitudinal data analysis; crude CD4% model included main effects for time (spline at 7.5 mo) and rural; adjusted model included additional terms for age at ART initiation, sex, and pre-ART WAZ.

[b]Results from longitudinal data analysis; crude WAZ model included main effects for time and rural and an interaction between time and rural; adjusted model included additional terms for pre-ART CD4%, age at ART initiation, sex, and self-reported diarrhea at each follow-up visit.

Weight Gain

WAZ improved steadily for both urban and rural children (Fig. 3). Median changes in WAZ after 6, 12, 18 and 24 months of treatment were 0.52 (IQR: -0.37, 1.34), 0.63 (IQR: -0.07, 1.71), 0.64 (IQR: 0.04, 1.66), and 0.81 (IQR: -0.04, 1.92), respectively, with no significant differences by location.

In a longitudinal model (Table 2), rural children initiated ART at a significantly lower WAZ, but improved at a significantly faster rate than urban children. These findings remained after adjusting for age, sex, and $CD4^+$ T-cell percentage at ART initiation, and self-reported diarrhea at the clinical visits. The proportion of children who were underweight decreased over time, but remained higher among rural children at 6, (52% vs. 39%), 12 (53% vs. 34%), 18 (43% vs. 26%) and 24 months (43% vs. 29%), although these differences were not statistically significant.

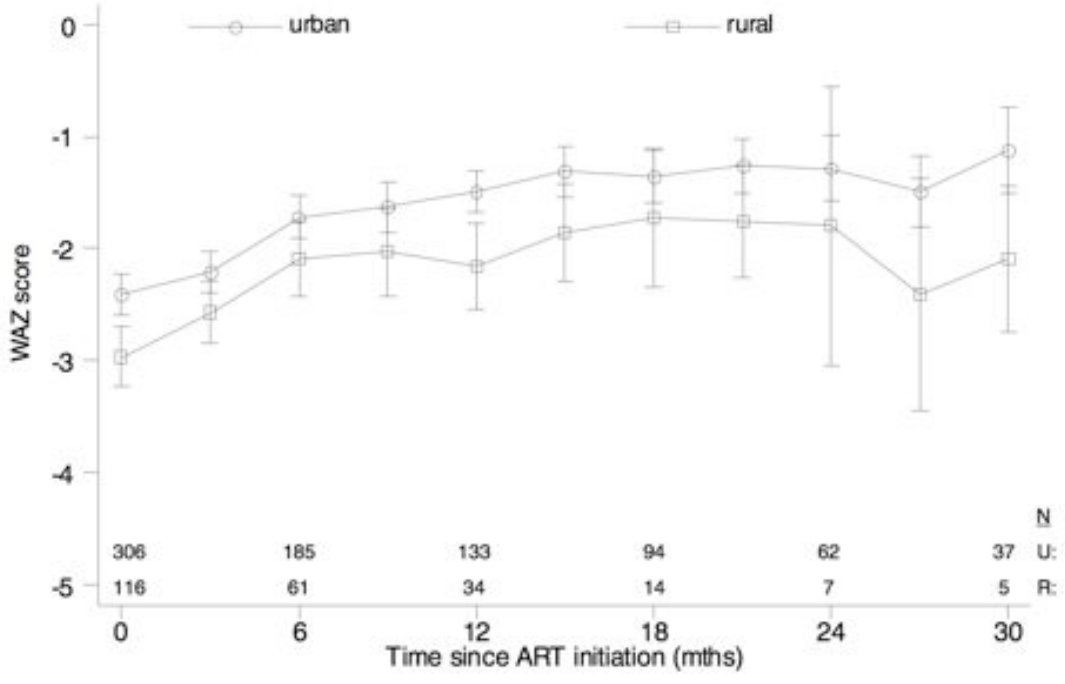

Figure 3. Mean (95% CI) weight-for-age z-score after treatment initiation among HIV-infected children in rural and urban Zambia.

Survival

Fifty-four (9%) children died during follow-up after a median of 63 days (IQR: 25, 170) on treatment. The overall mortality rate was 6.94 deaths per 100 person-years (PY) (95% confidence interval [CI]: 5.31, 9.06); it was significantly higher among rural (13.53 deaths per 100 PY; 95% CI: 8.82, 20.75) than urban children (5.30 deaths per 100 PY; 95% CI: 3.77, 7.45) (P = 0.0007). The probability of survival at 6, 12, and 24 months was 94% (95% CI: 91, 96), 93% (95% CI: 89, 95) and 90% (95% CI: 87, 93) among urban children, respectively, and 88% (95% CI: 81, 92), 85% (95% CI: 78, 90) and 84%

(95% CI: 75, 89) among rural children (log-rank test: *P* = 0.03) (Fig., Supplemental Digital Content 4, http://links.lww.com/INF/A519).

Mortality rates were significantly higher in the first 90 days of treatment for both rural and urban clinics (incidence rate ratio: 6.31; 95% CI: 3.56, 11.27), with 56% of deaths occurring in this time period. The mortality rate in the first 90 days was 19.35 deaths per 100 PY (95% CI: 12.19, 30.72) in the urban clinics and 33.59 deaths per 100 PY (95% CI: 19.08, 59.15) in the rural clinics (*P* = 0.07). The mortality rate after 90 days of treatment was 2.83 deaths per 100 PY (95% CI: 1.71, 4.69) in the urban clinic and 7.53 deaths per 100 PY (95% CI: 3.92, 14.47) in the rural clinics (*P* = 0.01).

Factors associated with higher risk of mortality included attending a rural clinic (Hazard Ratio [HR]: 1.86; 95% CI: 1.07, 3.22), younger age (0–2 years vs. ≥5 years: HR: 3.93; 95% CI: 2.16, 7.16), lower WAZ (<-3 vs. ≥2: HR: 4.94; 95% CI: 2.05, 11.90), WHO stage 3 or 4 (HR: 3.10; 95% CI: 1.31, 7.35), and low (<5%) CD4 T-cell percentage (HR: 1.86; 95% CI: 0.89, 3.89) at ART initiation. Adjusting for these factors, attending a rural clinic was no longer statistically significant (HR: 1.70; 95% CI: 0.85, 3.38).

Discussion

We identified important similarities and differences in the care and treatment of HIV-infected children in urban and rural Zambia. Characteristics at initial evaluation provide an indication of the stage of disease when children present for care. Urban children were older and presented at a more advanced clinical and immunologic stage of disease, although the majority of both urban and rural children presented with advanced disease and immune suppression, consistent with findings from other pediatric studies in sub-Saharan Africa [10,26]. The more advanced disease at presentation in the urban areas was unexpected, and persisted even within age strata (data not shown). These findings are contrary to similar comparisons of urban, peri-urban and rural adults [18,19]. The higher levels of malnutrition and longer travel distances in the rural areas are consistent with other studies in the region [2,7,27,28]. Long distances to travel in the rural areas influenced the timing of visits as well as program attrition, as loss to follow-up was high among children living farther away from the clinics, particularly among children ineligible for treatment. This effect was more pronounced in rural areas and remains a challenge in this setting.

Assessing time to ART initiation among eligible children provides an estimate of the time to fulfill requirements to initiate ART. The longer time to initiation in the rural clinics could not be explained by the characteristics of the children but could be explained by differing clinic procedures. In the rural clinics, distance was a recognized barrier and, when possible, efforts were made to synchronize visits between children and their caregivers, resulting in longer intervals between visits (data not shown). The time to ART initiation among ineligible children may provide a measure of how quickly children progress once evaluated, although this interval is composed of both the time to ART eligibility and initiation. No differences were found between urban and rural children. However, if the longer time from eligibility to initiation still applies to ineligible rural children, this finding might suggest more rapid disease progression, potentially due to a younger, more malnourished population. Once these factors were accounted for, a longer time to ART initiation was observed among rural children, lending support to this hypothesis.

Both urban and rural children responded well to treatment, consistent with other studies [10].

However, the level of immunologic and clinical response was influenced by their differing baseline characteristics. For immunologic response, children in the urban clinic initiated ART with a lower $CD4^+$ T-cell percentage and this difference persisted throughout treatment, resulting in a lower percentage of children achieving complete immune reconstitution. This was partially explained by the older urban population, as older children with higher levels of immunodeficiency have poorer immunologic responses to ART [20]. Mortality was consistently higher in the rural clinics, in part due to younger age and higher levels of malnutrition, and was higher than that reported by the KIDS-ART-LINC collaborative study in sub-Saharan Africa [26]. However, loss to follow-up was higher in the urban clinic and was associated with the same risk factors as mortality (data not shown). Studies among adults receiving ART found that almost half of those lost to follow-up had died [29]; therefore, it is possible that the increased mortality in the rural areas was due to more successful contact tracing and ascertainment of outcome.

These findings have several limitations. First, as data were collected from medical records, limited information was available on household and caregiver characteristics, which could have accounted for observed differences. Second, adherence data were not available from all clinics and therefore could not be evaluated. It is unknown whether adherence differs between urban and rural children and accounts for any observed differences in treatment outcome. Third, this research was conducted in 3 clinics and the profile of children and their treatment outcomes may not be representative of experiences in other urban and rural clinics in Zambia or sub-Saharan Africa. Results from the urban government clinic were similar to those reported from the 18 government facilities administered by CIDRZ (Centre for Infectious Disease Research in Zambia) in Lusaka [20], and may therefore be representative of the ART experience in Lusaka and other urban areas of Zambia. In contrast, the 2 rural clinics were from faith-based health facilities, which may have different support and healthcare personnel than government clinics and may therefore not be representative of all rural clinics in Zambia.

Despite these limitations, these findings demonstrate the feasibility of implementing pediatric ART programs in rural sub- Saharan Africa and support the continued expansion of ART programs to increase access to HIV services and reduce inequities [7]. Efforts should be made to improve the quality of HIV services, identify HIV-infected infants, promote earlier ART initiation, and strengthen links between HIV prevention, pediatric, and ART programs.

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Part Three:
Treatment responses in rural Zambia

Chapter 5

HIV-Infected Children in Rural Zambia Achieve Good Immunologic and Virologic Outcomes Two Years after Initiating Antiretroviral Therapy

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Abstract

Background: Many HIV-infected children in sub-Saharan Africa reside in rural areas, yet most research on treatment outcomes has been conducted in urban centers. Rural clinics and residents may face unique barriers to care and treatment.

Methods: A prospective cohort study of HIV-infected children was conducted between September 2007 and September 2010 at the rural HIV clinic in Macha, Zambia. HIV-infected children younger than 16 years of age at study enrollment who received antiretroviral therapy (ART) during the study were eligible. Treatment outcomes during the first two years of ART, including mortality, immunologic status, and virologic suppression, were assessed and risk factors for mortality and virologic suppression were evaluated.

Results: A total of 69 children entered the study receiving ART and 198 initiated ART after study enrollment. The cumulative probabilities of death among children starting ART after study enrollment were 9.0% and 14.4% at 6 and 24 months after ART initiation. Younger age, higher viral load, lower CD4+ T-cell percentage and lower weight-for-age z-scores at ART initiation were associated with higher risk of mortality. The mean CD4+ T-cell percentage increased from 16.3% at treatment initiation to 29.3% and 35.0% at 6 and 24 months. The proportion of children with undetectable viral load increased to 88.5% and 77.8% at 6 and 24 months. Children with longer travel times (≥5 hours) and those taking nevirapine at ART initiation, as well as children who were non-adherent, were less likely to achieve virologic suppression after 6 months of ART.

Conclusions: HIV-infected children receiving treatment in a rural clinic experienced sustained immunologic and virologic improvements. Children with longer travel times were less likely to achieve virologic suppression, supporting the need for decentralized models of ART delivery.

Introduction

More than 90% of the 2 million children living with HIV worldwide reside in sub-Saharan Africa [1]. With increasing evidence that pediatric treatment programs in resource-poor settings can achieve treatment outcomes comparable to those of developed countries [2,3], most countries in sub-Saharan Africa have implemented policies to increase access to antiretroviral therapy (ART). However, considerable inequities in access to treatment remain [4], as most HIV services are concentrated in urban areas distant from where many HIV-infected children reside.

Rural clinics and residents face unique barriers to care and treatment. Shortages of health care personnel, equipment and drugs may more heavily affect rural clinics, and several studies identified limited modes of transportation and food security as factors affecting the ability of rural residents to access care and treatment [5,6,7,8]. These factors may impact treatment responses of children. A recent study comparing HIV-infected children receiving ART in urban and rural Zambia found higher levels of undernutrition and mortality throughout treatment in the rural clinics [9]. To minimize barriers to care, different models of service delivery have been implemented in rural areas to increase accessibility of ART, including the use of nurses [10,11,12,13,14,15] and general practitioners [16] in the provision of ART at primary care clinics, and home-based care provided by trained field officers [17] and volunteers [18]. Consequently, evaluation of treatment programs and treatment outcomes in rural settings is needed. Several reports are available from rural programs [10,12,13,14,15,16,17,18,19], but few focus on children [5,11].

This observational cohort study reports immunologic and virologic treatment outcomes and mortality among HIV-infected children receiving up to two years of treatment at a rural HIV clinic in Macha, Zambia.

Materials and Methods

Ethics Statement

The study was approved by the Ministry of Health in Zambia, the Research Ethics Committee of the University of Zambia and the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health. Written informed consent was obtained from parents or guardians and assent was obtained from children 8–16 years of age.

Study setting and population

The study was conducted at Macha Hospital in rural Southern Province, Zambia. The study setting has been described in detail elsewhere [5]. Briefly, the catchment area of Macha Hospital is populated primarily by traditional villagers living in small, scattered homesteads. Macha Hospital is a 208-bed district-level referral hospital administered by the Zambian Brethren in Christ Church that functions within the healthcare system of the Ministry of Health. Since 2005, Macha Hospital has been one of the primary ART providers in the district and has cared for over 6000 HIV infected adults and children through the Government of Zambia's antiretroviral treatment program, with additional support from the President's Emergency Plan for AIDS Relief (PEPFAR) through the non-governmental organization AidsRelief.

HIV-infected children are referred to the clinic from voluntary counseling and testing programs, in- and outpatient clinics, and rural health centers. Since February 2008, children born to HIV-infected women are routinely tested for HIV infection at approximately 6 weeks of age using dried blood spot samples transported to Lusaka, Zambia for HIV DNA PCR. Clinical care is provided without charge by medical doctors and clinical officers, and adherence counseling by nurses and trained counselors. Eligibility for ART is determined based on WHO treatment guidelines [20,21]. The first-line antiretroviral treatment regimen consists of two nucleoside reverse transcriptase inhibitors (lamivudine plus zidovudine, stavudine or abacavir) and a non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine). Fixed dose pediatric combinations of lamivudine and stavudine are available, as well as Triomune® baby and junior.

Study procedures

HIV-infected children younger than 16 years of age seeking care at the antiretroviral treatment clinic at Macha Hospital were eligible for enrollment into a prospective, observational cohort study beginning in September 2007. Children were evaluated at study visits approximately every three months, at which time a questionnaire was administered to the guardian, the child was examined and a blood specimen was obtained. The questionnaire included information on demographic information, household characteristics, medical history, HIV-related stigma and adherence for children receiving treatment. Adherence was measured at each visit by pill count for children receiving pills and by weight for children receiving syrups. Blood specimens were collected in EDTA tubes. As part of routine clinical care, CD4+ T cell counts and percentages were measured using the Guava Easy CD4 system (Guava Technologies, Inc., Hayward, CA). As part of study procedures, plasma levels of HIV RNA were quantified by a reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor v. 1.5, Roche Molecular Systems; lower limit of detection: 400 copies/mL). Viral load testing was only performed for children who started ART after study enrollment and was performed on batched samples; therefore, results were not available for clinical care. Information prior to study enrollment was abstracted from medical records. Home visits were attempted for children who missed study visits. For children who died, the location and cause of death were ascertained through verbal autopsy or through hospital or clinic records.

Statistical analysis

For the present analysis, all children enrolled in the study and receiving ART between September 2007 and September 2010 were included. This study sample consisted of two groups of children: 1) children receiving ART at study enrollment (Group A); and 2) children who were treatment-naïve at study enrollment and initiated ART during the specified period (Group B). Children were included in the analysis until they died, were lost to follow-up or were administratively censored at September 1, 2010 or 24 months of ART. Children whose last study visit occurred more than 6 months prior to September 1, 2010 were considered lost to follow-up.

Data were entered in duplicate using EpiInfo (Centers for Disease Control and Prevention) and analyses were conducted in SAS for Windows version 9.1 (SAS Institute Inc., Cary, NC) and STATA, version 9 (StataCorp LP, College Station, Texas). Characteristics at study enrollment and ART initiation were compared between groups of children. The Wilcoxon rank sum test was used to compare continuous variables and the chi-square test was used to compare categorical variables. A measure of socio-economic status (SES) was calculated based on the Demographic and Health Survey SES scale used in Zambia [22]. SES percentiles were based on the predetermined cut offs

(<25th=0–6; 26–50th=7–12; 51–75th=13–18; >75th=19–24). Weight-for-age z-scores were calculated based on the WHO growth standards [23] and children with z-scores below -2 were defined as underweight. Severe immunodeficiency was defined by age according to the 2006 WHO treatment guidelines [20], and severe anemia was defined as haemoglobin concentration <8 g/dL [24]. If laboratory tests were not available from the visit at which ART was initiated, results were used within 3 months prior to the date of initiation.

Risk factors for mortality after ART initiation were evaluated using Cox proportional hazards models. Time since ART initiation was used as the time axis, and late entries were used for children in Group A. Risk factors at ART initiation of interest included age, sex, orphan status, travel time to the clinic, CD4+ T-cell percentage, WAZ, anemia and viral load. Factors associated with mortality ($p<0.10$) in the univariable models were eligible for inclusion in the multivariable model.

Immunologic and virologic treatment outcomes as well as adherence were assessed. For all outcomes, children were included if they had at least one post-ART measure available. To report outcomes at specific time points, measurements were aggregated to within 45 days. Immunologic treatment outcomes were evaluated using linear mixed effects models with random intercept, exchangeable correlation structure and robust standard error estimation. A spline term was added at 7.5 months, the upper window around the 6-month measure. Adherence was calculated for each drug returned and is reported as the percentage of medication returned of the expected use since the prior visit. For children taking more than one drug, the minimum adherence of all drugs was calculated. Adherence measures were capped at 100%. Both continuous and categorical measures of adherence are reported. For the categorical measure, a child was defined as adherent if they took more than 95% of the prescribed doses. Predictors of viral suppression between 6 and 24 months after ART initiation were assessed among children in group B. As children could contribute more than one measure of viral load, repeated measures logistic regression models were fit with generalized estimating equations. Predictors of interest included age, sex, orphan status, education of the primary caregiver, socioeconomic status, travel time, ART regimen, underweight and severe immunodeficiency at ART initiation. Adherence and the presence of others in the household receiving ART were also assessed at the time of each viral load measure. As the sample size was small, separate multivariable models were built for each predictor found to be associated with viral suppression ($p<0.10$) in the univariable models. Only factors associated with the predictor of interest were included in each multivariable model.

Results

Characteristics of the study population at study enrollment and ART initiation

Between September 2007 and September 2010, 267 children received ART, including 69 children who entered the study already receiving ART (Group A) and 198 children who initiated ART after study enrollment (Group B). Children in Group A entered the study a median of 8.0 months (interquartile range [IQR]: 2.3, 12.9) after initiating ART, while children in Group B initiated ART a median of 1.7 months (IQR: 0.9, 5.0) after study enrollment. The median follow-up time in the study was 14.9 months (IQR: 5.0, 19.2) for children in group A and 11.8 months (IQR: 4.4, 20.7) for children in group B.

Table 1. Characteristics at study enrolment and ART initiation of HIV-infected children receiving antiretroviral therapy

	Total (n=267)	Group A (n=69)	Group B (n=198)	p-value
Study enrolment				
Median age in years (IQR)	2.67 (1.41, 6.38)	3.80 (2.26, 8.54)	2.21 (1,27, 5.26)	0.001
<2 yrs	104 (39.0)	14 (20.3)	90 (45.5)	
2-5 yrs	86 (32.2)	29 (37.7)	57 (28.8)	
≥5 yrs	77 (28.8)	26 (37.7)	51 (25.8)	0.001
Male sex (%)	131 (49.1)	41 (59.4)	90 (45.5)	0.05
Mother received PMTCT (%)	15 (5.3)	1 (1.5)	13 (6.6)	0.19
Vital status of parents (%)				
Both alive	189 (72.1)	41 (62.1)	148 (75.5)	
One parent died	52 (19.9)	15 (22.7)	37 (18.9)	
Both died	21 (8.0)	10 (15.2)	11 (5.6)	0.03
Travel times (hours) (%)				
<1	24 (9.1)	6 (9.1)	18 (9.1)	
1-2	80 (30.4)	21 (31.8)	59 (30.0)	
3-4	88 (33.5)	19 (28.8)	69 (35.0)	
≥5	71 (27.0)	20 (30.3)	51 (25.9)	0.80
ART Initiation				
Median age in years (IQR)	2.73 (1.57, 6.73)	2.90 (1.71, 7.75)	2.69 (1.50, 5.92)	0.37
<1 yrs	39 (14.6)	10 (14.5)	29 (14.7)	
1-1.9 yrs	59 (22.1)	12 (17.4)	47 (23.7)	
2-4.9 yrs	87 (32.6)	23 (33.3)	64 (32.3)	
≥5yrs	82 (30.7)	24 (34.8)	58 (29.3)	0.69
Median WAZ (IQR)[a]	-2.28 (-3.37, -1.39)	-2.48 (-3.64, -1.72)	-2.16 (-3.22, -1.34)	0.10
Underweight (%)	120 (56.6)	34 (66.7)	86 (53.4)	0.10
Missing (%)	55 (20.6)	18 (26.1)	37 (18.7)	
Median CD4% (IQR)	15.9 (10.5, 20.1)	13.1 (9.4, 16.2)	16.8 (10.9, 20.6)	0.03
Severe immunodeficiency (%)[b]	140 (63.1)	28 (73.7)	112 (60.9)	0.14
Missing (%)	45 (16.9)	31 (44.9)	14 (7.1)	

Group A: children who entered the study already receiving ART; Group B: children who initiated ART after study enrolment.
[a] Among children <10 years of age.
[b] Defined by age according to the 2006 WHO guidelines.

The median age of children at enrollment into the ART clinic was 2.76 years (IQR: 1.42, 7.67) among children in Group A and 2.03 years (IQR: 1.11, 4.95) among children in Group B (p = 0.07). The median age of children at study enrollment was 3.80 years (IQR: 2.26, 8.54) among children in Group A and 2.21 (IQR: 1.27, 5.36) in Group B, and 49.1% were male (Table 1). At ART initiation, the median age was 2.90 years (IQR: 1.71, 7.75) in Group A and 2.69 (IQR: 1.50, 5.92) in Group B. The proportion of children who were underweight at ART initiation was 66.7% and 53.4% among children in Group A and B, respectively. The proportion of children with severe immunodeficiency was 73.7% and 60.9% among children in Group A and B, respectively.

Few mothers reported receiving antiretroviral drugs to prevent mother-to-child transmission (5.3%). Children were primarily cared for by a parent (78.4%), although 27.9% reported that at least one parent had died. Other primary caregivers included grandparents (11.7%) and aunts or uncles (7.2%). The education level of the primary caregiver was low, with 5.7% reporting no education and 58.5% reporting no more than a primary school education, 52.1% of whom completed grade 7.

Only 35% reported a secondary school education. In addition, 80.9% of caregivers reported being able to read either Tonga or English. The majority (65.8%) of children lived in households with a SES in the lowest quartile and 30% lived in households with a SES in the second lowest quartile. Children who initiated ART prior to study enrollment were more likely to be male, to have lost both parents, and to have initiated ART with a lower median CD4+ T-cell percentage (Table 1).

Mortality

Within the first two years after ART initiation, 27 children (10.1%) died (Group A: 5 (7.3%); Group B: 22 (11.1%); p = 0.36), 13 children (4.9%) transferred to another clinic (Group A: 2 (2.9%); Group B: 11 (5.6%); p=0.38), and 4 children (1.5%) defaulted (Group A: 1 (1.5%); Group B: 3 (1.5%); p = 0.97). The proportion of children who defaulted among those enrolled for more than 6 months prior to September 1, 2010 was 1.7%. The majority of deaths occurred within the first few months of starting ART. Among children initiating ART after study enrollment (Group B), the median time to death from ART initiation was 3.08 months (IQR: 0.59, 6.33). Among all children, the cumulative probabilities of death were 9.0% (95% CI: 5.8, 13.9), 12.0% (95% CI: 8.1, 17.5) and 14.4% (95% CI: 9.9, 20.6) at 6, 12, and 24 months after ART initiation, respectively. Information on cause of death was available for 18 children.

Table 2. Risk factors for mortality after initiation of antiretroviral treatment

Characteristics at ART initiation	**Crude Hazard ratio (95% CI)**	**Adjusted hazard ration (95%CI)**
Female	1.03 (0.48, 2.20)	
Age	0.79 (0.66, 0.95)	0.40 (0.22, 0.74)
<1 yr	8.72 (1.79, 42.47)	
1-1.9 yrs	9.81 (2.21, 43.66)	
2-4.9 yrs	2.44 (0.47, 12.58)	
≥5 yrs	1	
Orphan	0.68 (0.26, 1.79)	
Travel time		
<1 hr	1	
1-2 hrs	2.91 (0.37, 22.96)	
3-4 hrs	2.22 (0.28, 17.57)	
≥5 hrs	2.93 (0.37, 23.48)	
WAZ[a]	0.55 (0.43, 0.72)	0.64 (0.48, 0.86)
≥-2	1	
-2.1 to -3	3.68 (0.67, 20.13)	
<-3	10.96 (2.49, 48.25)	
Hemoglobin <8 g/dL	1.97 (0.66, 5.91)	
CD4 % (per 5 points)	0.77 (0.56, 1.05)	0.67 (0.44, 1.02)
Severe immunodeficiency[b]	1.23 (0.49, 3.08)	
Viral load >750,000 copies/mL[c]	19.35 (2.31, 161.90)	3.03 (0.31, 25.58)

[a] Among children <10 years of age
[b] Defined by age according to the 2006 WHO guidelines.
[c] An indicator for missing viral loads was included in the multivariable model as viral load at ART initiation was only available on a subset of children.

Contributing factors included diarrhea (n = 9), malnutrition (n = 8), tuberculosis (n = 5), pneumonia (n = 5), meningitis (n = 2), cerebral malaria (n = 1), encephalopathy (n = 1), and possible Kaposi's sarcoma (n = 1). Location of death was available for 21 children. Ten children died in the hospital (47.6%), two children died on the way to the hospital (9.5%), one child died in the rural health center (4.8%), and eight children died at home (38.1%). Younger age, lower WAZ, lower CD4+ T-cell percentage and high viral load (>750,000 copies/mL) at ART initiation were associated with a higher risk of mortality (Table 2). Only younger age and lower WAZ remained significantly associated with higher mortality after adjusting for other factors.

Immunologic and virologic treatment outcomes

Among children with at least one post-ART measure, immunologic and virologic treatment outcomes improved within three to six months of starting ART (Table 3). Mean CD4+ T-cell percentage increased from 16.3% at treatment initiation to 29.3%, 33.9%, 33.0% and 35.0% at 6, 12, 18 and 24 months on ART. Consequently, the proportion of children with a CD4+ T-cell percentage >25% increased from 10.9% at treatment initiation to 66.7%, 81.5%, 84.5% and 87.5% at 6, 12, 18, and 24 months on ART. Results of the longitudinal models indicated that CD4+ T-cell percentage increased by 1.80 (standard error [SE]: 0.088; p-value ≤0.0001) percentage points per month in the first 6 months, and then increased by 0.23 (SE: 0.058; p-value ≤0.0001) percentage points per month thereafter.

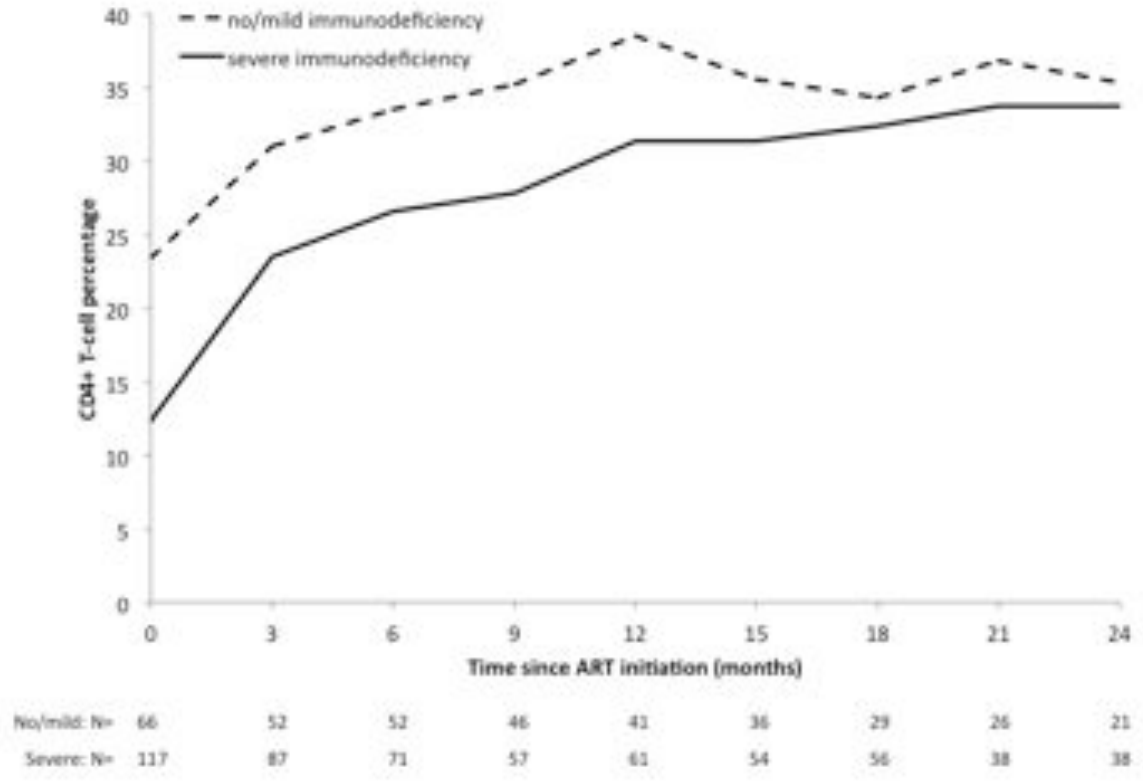

Figure 1. Mean $CD4^{+}$ T-cell percentage (95% CI) after ART initiation, by level of immunodeficiency at initiation.

No difference in the pattern of improvement was found by age, sex or underweight status at ART initiation. Monthly increases in CD4+ T-cell percentages in children with severe immunodeficiency at ART initiation were significantly greater than in children without severe immunodeficiency, both within the first 6 months (2.04 [SE: 0.11], p-value ≤0.0001 vs. 1.60 per month [SE: 0.15] p-value ≤0.0001; p-interaction = 0.02) and after 6 months of ART (0.30 [SE: 0.09], p-value = 0.001 vs. 0.075 [SE: 0.07], p-value = 0.28; p-interaction = 0.04) (Figure 1).

Median viral load decreased rapidly after the start of ART, from 5.4 log copies/mL at treatment initiation to <2.6 log copies/mL throughout treatment (Table 3). The proportion of children with undetectable viral load increased to 90.0%, 88.5%, 88.3%, 86.8% and 77.8% at 3, 6, 12, 18 and 24 months on ART. One hundred and four children received ART for at least 6 months, 90 (87%) of whom had persistent undetectable viral loads at or beyond 6 months of ART. Fourteen children (13%) had at least one sample with detectable viral load, of whom 4 (29%) had persistent detectable viral load, 3 (21%) had detectable viral load at more than one visit, 6 (43%) had viral rebound which then remained undetectable, and 1 (7%) had a detectable viral load on their last available sample.
The 4 children with persistent detectable viral load had no evidence of clinical or immunologic failure, and no children in group B were switched to a second line regimen due to treatment failure during the study period. One child in group A was switched to a second line regimen including a protease inhibitor due to clinical and immunologic failure 20.7 months after initiation.

Table 3. Immunologic and virologic outcomes and adherence by time on treatment.

	Treatment	**3 months**	**6months**	**12 months**	**18 months**	**24 months**
Immunologic outcome	*N=183*	*N=149*	*N=135*	*N=119*	*N=97*	*N=72*
Mean CD4% (STD)	16.3 (7.6)	26.6 (11.0)	29.3 (10.4)	33.9 (9.6)	33.0 (9.0)	35.0 (8.5)
Mean change in CD4% from ART initiation (STD)	_	9.4 (8.9)	12.4 (8.5)	17.4 (8.8)	17.3 (9.9)	19.0 (9.2)
% with CD4% >25%	10.9	54.4	66.7	81.5	84.5	87.5
% missing, of those in care[a]	7.8	27.7	25.0	23.7	20.5	20.0
Virologic outcome[b]	*N=106*	*N=100*	*N=96*	*N=77*	*N=53*	*N=27*
Median log VL (IQR)	5.4 (5.0, 5.9)	2.6 (2.6, 2.6)	2.6 (2.6, 2.6)	2.6 (2.6, 2.6)	2.6 (2.6, 2.6)	2.6 (2.6,2.6)
Median change in log VL from ART initiation (IQR)	_	-2.7 (-3.3, -2.2)	-2.7 (-3.3, -2.1)	-2.6 (-3.3, -1.8)	-2.6 (-2.8, -1.8)	-2.4 (-2.7, -1.1)
% with undetectable VL	_	90.0	88.5	88.3	86.8	77.8
% missing, of those in care[a]	46.5	45.1	35.1	29.4	30.3	34.1
Adherence		*N=150*	*N=133*	*N=115*	*N=87*	*N=71*
Median (IQR)		98.5 (89,100)	98 (93, 100)	99 (96, 100)	100 (96, 100)	99 (95, 100)
% ≤95%		35.3	32.3	23.5	24.1	25.4
% missing, of those in care[a]		27.2	26.1	26.3	28.7	21.1

Note: Immunologic and virologic treatment outcomes were evaluated among children with at least one post-ART measure available.
[a] Children in care were defined as those who were enrolled in the study and presented to the clinic at the specified visit or, if the visit was missed, at any subsequent visit.
[b] The analysis was restricted to children in group B for the virologic outcome.

Adherence

Adherence data were available for at least one study visit for 216 children (Group A: 55; Group B: 161). Estimated adherence, defined as the minimum adherence of all drugs taken, over the study period was high, with a median of 98–100% at all time points up to 24 months after treatment initiation (Table 3). The proportion of children who were non-adherent (adherence percentage less than 95%) decreased over time, from 35.3% at 3 months to 25.4% at 24 months. We examined patterns of adherence over time to determine if the same children were consistently non-adherent. Among the 172 children who had at least 2 adherence measures at study visits, 74 (43%) were consistently adherent, 3 (2%) were consistently non-adherent, and 95 (55%) had patterns alternating between adherence and non-adherence.

Table 4. Predictors of viral suppression after 6 months of antiretroviral therapy.

	Crude odds ratio (95% CI)	**Adjusted odds ratio (95% CI)**
Characteristics at ART initiation		
Female	0.69 (0.25, 1.94)	
Age		
<1 yr	0.32 (0.05, 2.07)	1.01 (0.05, 2.82)
1 - 1.9 yrs	0.16 (0.03, 0.84)	0.85 (0.14, 4.95)
2 - 4.9 yrs	0.39 (0.07, 1.98)	1.08 (0.10, 11.35)[d]
≥5 yrs	1	1
Orphan	7.22 (1.61, 32.45)	3.32 (0.64, 17.30)[e]
Travel time		
<1 hr	1	1
1-2 hrs	0.34 (0.04, 3.16)	0.51 (0.07, 3.86)
3-4 hrs	0.20 (0.03, 1.65)	0.36 (0.05, 2.37)
≥5 hrs	0.10 (0.01, 0.82)	0.17 (0.02, 1.19)[e]
High SES (>50th percentile)	2.28 (0.35, 15.00)	
Education of primary caregiver		
None / Primary school	1	
Secondary school / university	1.22 (0.40, 3.78)	
Underweight[a]	0.87 (0.28, 2.68)	
Severe immunodeficiency[b]	0.70 (0.24, 2.03)	
High viral load (>750,000 copies /mL)[c]	0.60 (0.17, 2.04)	
ART regimen including stavudine	0.47 (0.15, 1.48)	
ART regimen including nevirapine	0.35 (0.46, 0.98)	0.33 (0.11, 1.03)[f]
ART regimen including fixed dose combinations	2.30 (0.65, 8.10)	
Characteristics at each viral load measure		
Other people in the household on ART	0.78 (0.48, 1.27)	

[a] Among children <10 years of age
[b] Defined by age according to the 2006 WHO guidelines
[c] An indicator for missing viral load was included in the multivariable model as viral load at ART initiation was only available on a subset of children
[d] Multivariable model included orphan status, travel time, nevirapine and age at ART initiation.
[e] Multivariable model included orphan status, travel time and age at ART initiation
[f] Multivariable model include age and nevirapine at ART initiation.

Adherence was not associated with any characteristics of the child or caregivers. Children taking ART regimens including fixed dose combinations were, however, less likely to be non-adherent (e.g. 45.2% of children taking individual drugs were non-adherent compared to 7.1% of children taking fixed dose combinations 9 months after ART initiation; p=0.01). Non-adherence was also marginally associated with a lower risk of achieving viral suppression (odds ratio: 0.68; 95% CI: 0.46, 1.01; p = 0.05).

Predictors of viral suppression after 6 months of ART

Longer travel time, younger age, non-orphan status and use of nevirapine at ART initiation were significantly associated with a lower risk of viral suppression (Table 4; Figure 2). These characteristics were correlated, as children with shorter travel times were more likely to be older and to be orphans. Children receiving nevirapine were also more likely to be younger. After adjustment, longer travel times and use of nevirapine remained marginally associated with a lower risk of viral suppression.

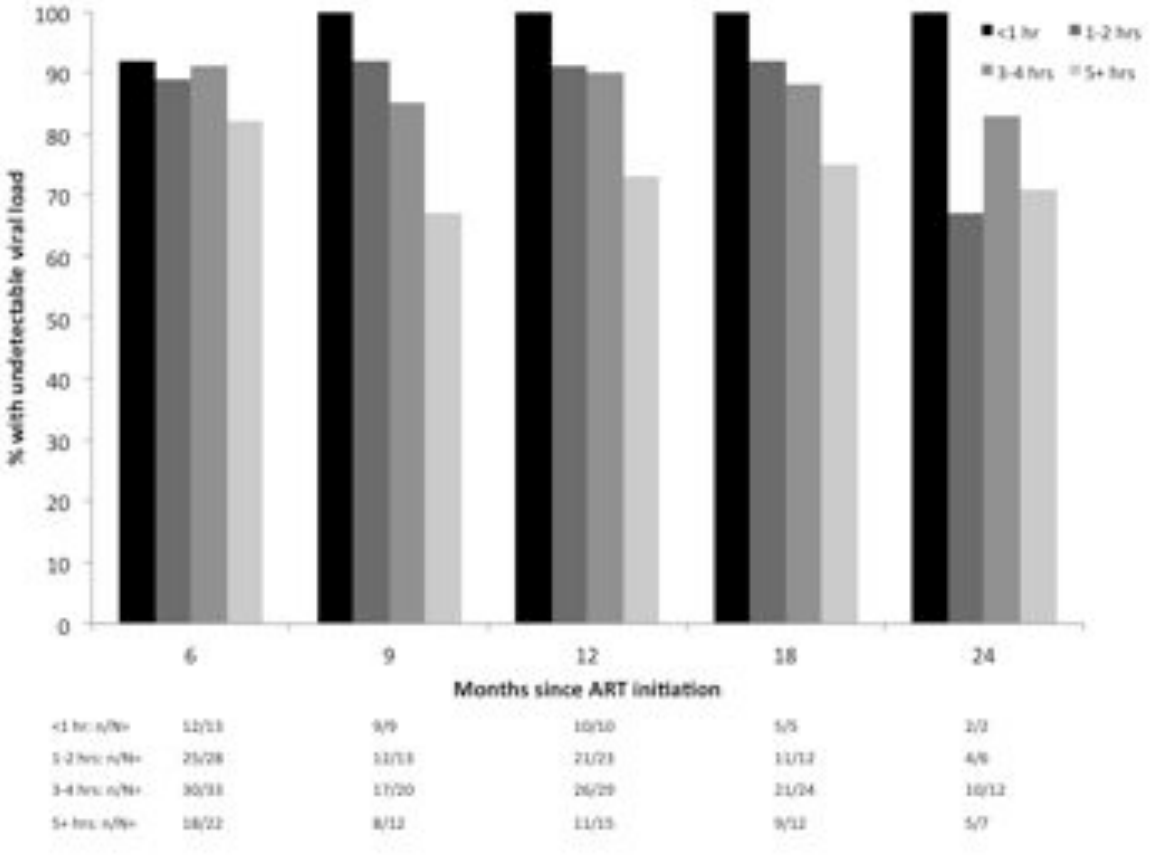

Figure 2. Percentage of children achieving viral suppression after 6 months of ART, by travel time.

Discussion

This study of treatment outcomes among HIV-infected children in Zambia demonstrated that ART could effectively be delivered in this rural setting and that these children responded well to treatment. Two groups of children were assessed, those who entered the study receiving ART and those who initiated ART during the study period. Children in the latter group were younger and had better clinical and immunological profiles. While the children receiving ART at study entry represented a subset of children who initiated ART at the clinic prior to the start of this study, these findings are consistent with a previous study in this population demonstrating improvements in the enrollment and treatment of children at younger ages and less severe stages of disease progression [25].

The proportion of children who died (14.4%) within 24 months of starting ART was higher than reported from other studies of children in sub-Saharan Africa. The KIDS-ART-LINC study in 17 sites across sub-Saharan Africa reported cumulative probabilities of mortality of 4.8%, 6.0% and 6.0% at 6, 12 and 24 months [26], respectively, while the International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) study across 10 sites in southern Africa reported probabilities of 4.5% and 7.7% at 12 and 36 months [27,28], respectively. This difference may partially be explained by the relatively younger and more undernourished rural population in this study, as both of these factors are associated with higher mortality [2]. However, the difference may also be explained by the lower observed loss to follow-up of 1.5% at 24 months in this study, compared to 10.3% in the KIDS-ART-LINC study over the same time period [26]. Among adults, approximately 40% of losses to follow-up represented unreported deaths [29]. In fact, when the IeDEA-SA study accounted for mortality among losses to follow-up, the 12 month mortality increased from 4.5% to 8.7% [28]. Consequently, the high mortality and low loss to follow- up in this study could also be due to more complete ascertainment of outcomes as a result of contact tracing. The majority of deaths occurred within the first 3 months of ART and were associated with younger age, lower WAZ, lower CD4+ T-cell percentage and higher viral load, consistent with other observations [2].

Children followed in this study achieved good immunologic and virologic treatment outcomes, such that 88% had a CD4+ T-cell percentage greater than 25% and 78% had an undetectable HIV viral load 24 months after initiating ART. Contrary to the results of an earlier cross-sectional analysis in this cohort [5], early gains in CD4+ T-cell percentages were maintained throughout follow- up. Similar improvements in immune status were observed in other African studies [2]. The level of viral suppression in this cohort, however, was higher than reported in many other studies of African children [2,27]. Few studies are available for comparison from rural areas, but one study in rural South Africa reported that 71% of children remaining on treatment after 12 months achieved viral suppression [30].

Correlates of viral suppression were explored, including established factors such as drug regimen and adherence, and factors related to treatment in a rural setting, such as travel time to the clinic. Clinical trials in adults [31,32] and observational studies in children [33,34,35] showed higher rates of virologic failure with nevirapine-based regimens compared to efavirenz-based regimens, consistent with our findings. Adherence in this cohort was high throughout treatment and was associated with viral suppression. However, despite being one of the main determinants of viral suppression after ART initiation, adherence has not consistently been found to correlate with viral

suppression in children [36,37,38], perhaps due to the difficulties in measuring adherence among children, including complex drug regimens, use of pills and syrups, and the potential involvement of multiple caregivers in the administering of medication [39]. This study attempted to overcome these difficulties by using a more objective measure of adherence by medication returns rather than self-report.

The main novel factor associated with viral suppression was travel time. As this was a rural population, participants travelled from surrounding villages to the clinic and over a quarter of the study population reported travelling five or more hours. Transportation and distance have been reported as barriers to care and treatment in this [5] and other adult and pediatric populations [6,7,8,40], as long travel distances or times incur a direct cost for transportation and indirect cost for time away from work and childcare. Distance to the clinic was associated with retention in this clinic, with children living farther away from the clinic more likely to be lost to follow-up [9]. However, this is the first report of an association between travel time and virologic outcome, with children travelling five or more hours significantly less likely to achieve viral suppression. This relationship is hypothesized to be due to the impact of travel time on the frequency of visits to the clinic and pharmacy. In this study, associations between travel time and missed or delayed visits as well as adherence were not found; however, information on pharmacy or clinic appointments in between study visits was not available. This finding should be confirmed in other populations as it has important implications for the treatment of HIV-infected children as treatment programs are increasingly implemented and scaled up in rural areas.

The main limitations of the study include the small sample size, particularly at longer follow-up times, and missing data on adherence and treatment outcomes, which may have led to an overestimation of the success of ART. However, this is one of the few pediatric studies conducted in rural sub-Saharan Africa, and the high proportion of children with available immunologic and virologic measures suggests minimal bias for these outcomes. In addition, children cared for at the Macha ART clinic benefit from being enrolled in a research study and attending a faith- based health facility, which may have higher levels of support and staffing than government clinics in the same region. While the study relied on laboratory tests (with the exception of viral load) and clinical measures performed as part of routine care to minimize this bias, the good treatment outcomes observed in this study may not be generalizable to other rural government clinics.

In summary, this study demonstrated that ART can effectively be delivered in a rural setting and that children experienced sustainable immunologic and virologic improvements after initiating ART. The observed detrimental effect of long travel times on virologic suppression may have implications for ART delivery in this setting. As treatment programs expand further into rural areas, clinic catchment areas will expand. Unless decentralized models of care are implemented, children may have to travel great distances for their care and treatment, which may impact both their ability to remain in care and respond to treatment.

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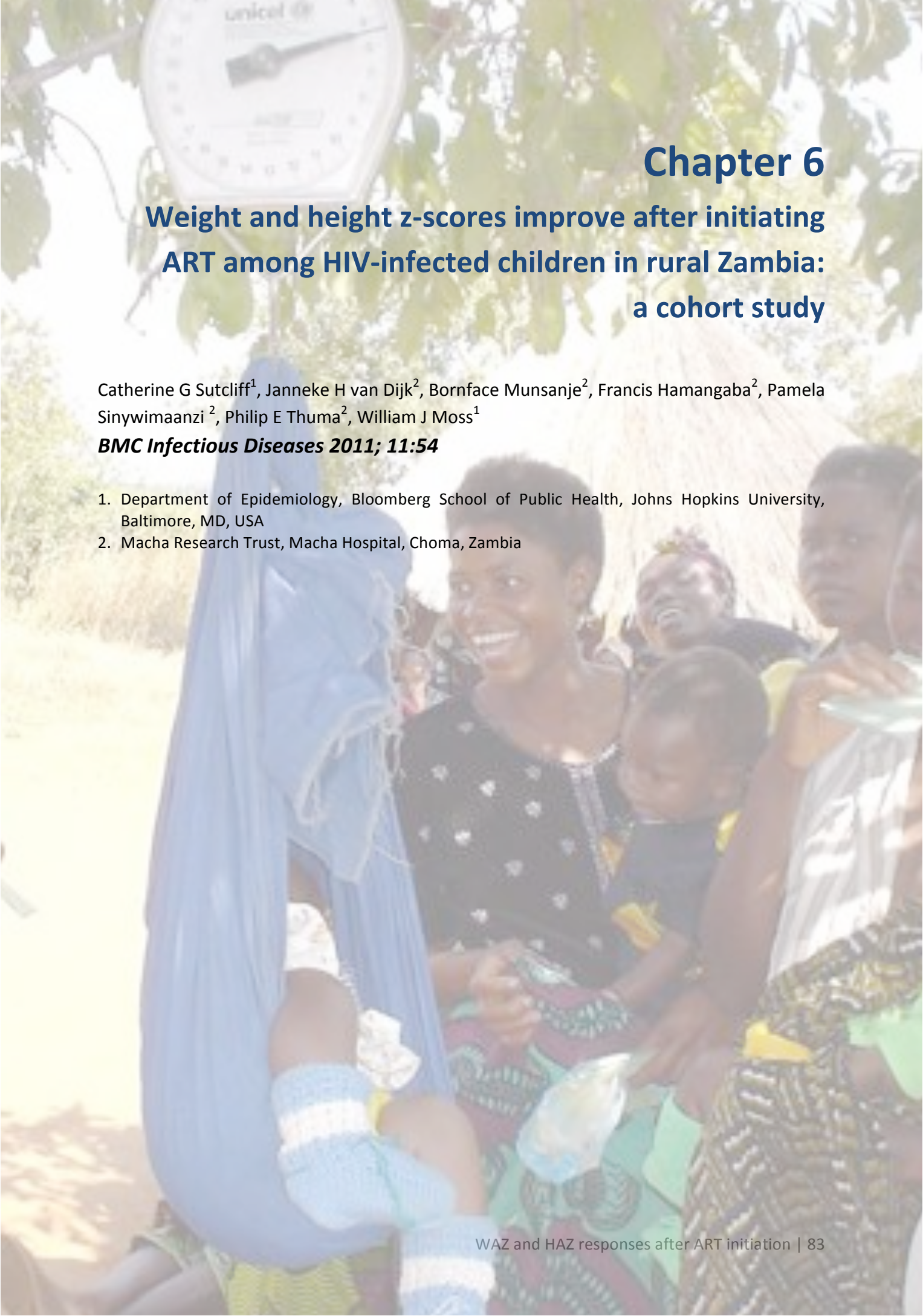

Chapter 6

Weight and height z-scores improve after initiating ART among HIV-infected children in rural Zambia: a cohort study

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Abstract

Background: Deficits in growth observed in HIV-infected children in resource-poor settings can be reversed with antiretroviral treatment (ART). However, many of the studies have been conducted in urban areas with older pediatric populations. This study was undertaken to evaluate growth patterns after ART initiation in a young pediatric population in rural Zambia with a high prevalence of undernutrition.

Methods: Between 2007 and 2009, 193 HIV-infected children were enrolled in a cohort study in Macha, Zambia. Children were evaluated every 3 months, at which time a questionnaire was administered, height and weight were measured, and blood specimens were collected. Weight- and height-for-age z-scores were constructed from WHO growth standards. All children receiving ART at enrollment or initiating ART during the study were included in this analysis. Linear mixed effects models were used to model trajectories of weight and height-for-age z-scores.

Results: A high proportion of study children were underweight (59%) and stunted (72%) at treatment initiation. Improvements in both weight- and height-for-age z-scores were observed, with weight-for-age z-scores increasing during the first 6 months of treatment and then stabilizing, and height-for-age z-scores increasing consistently over time. Trajectories of weight-for-age z-scores differed by underweight status at treatment initiation, with children who were underweight experiencing greater increases in z-scores in the first 6 months of treatment. Trajectories of height-for-age z-scores differed by age, with children older than 5 years of age experiencing smaller increases over time.

Conclusions: Some of the effects of HIV on growth were reversed with ART initiation, although a high proportion of children remained underweight and stunted after two years of treatment. Partnerships between treatment and nutrition programs should be explored so that HIV-infected children can receive optimal nutritional support.

Background

Children in sub-Saharan Africa have high levels of undernutrition, exhibiting lower weight- and height-for-age than children in high resource settings. Both of these conditions are exacerbated by HIV infection [1-4], and can be used to determine disease status and monitor treatment response [5]. As implementation of antiretroviral treatment (ART) programs in sub-Saharan Africa has increased [6], many HIV-infected children are benefitting from treatment and are experiencing reductions in morbidity and mortality. Several studies have shown that many of the deficits in growth due to HIV infection are reversed with ART, with children exhibiting consistent improvements in weight-for-age [7-19]. Some studies, but not all [12,13,17], have also reported improvements in height-for-age [7-10,14,16,18,19]. Gains in weight have been found to correlate with treatment response [19].

Many of these studies have been conducted in urban areas, where food security tends to be higher and levels of undernutrition lower than in surrounding rural areas [20]. In addition, many of these studies were conducted in the first years of program implementation when the majority of children initiating ART were older [21]. Both age [11] and level of undernutrition at treatment initiation [7] have the potential to impact growth trajectories and the effect of ART. Consequently, this study was undertaken to evaluate growth after ART initiation in a young pediatric population in rural Zambia and identify characteristics at ART initiation that influence growth trajectories.

Methods

Study setting and population

The study was conducted at Macha Hospital in a rural area of Southern Province, Zambia. The study setting and population have been described in detail elsewhere [22]. Briefly, Macha Hospital is a district-level referral hospital administered by the Zambian Brethren in Christ Church. Since 2005, Macha Hospital has provided care to over 6000 HIV-infected adults and children through the Government of Zambia's antiretroviral treatment program, with additional support from the President's Emergency Plan for AIDS Relief (PEPFAR) through the non-governmental organization, AidsRelief.

Children with a positive HIV serologic test are referred to the clinic from voluntary counseling and testing programs, outpatient clinics and rural health centers. Early infant diagnosis has been available since February 2008. Clinical care is provided without charge by medical doctors and clinical officers, and adherence counseling by nurses and trained counselors. ART is initiated according to WHO guidelines [23,24]. The first-line antiretroviral treatment regimen consists of two nucleoside reverse transcriptase inhibitors (lamivudine (3TC) plus zidovudine (AZT) or stavudine (D4T) or abacavir (ABC)) and a non-nucleoside reverse transcriptase inhibitor (efavirenz (EFV) or nevirapine (NVP)). Pediatric and adult fixed dose combinations of D4T and 3TC are available, as well as of D4T, 3TC and NVP. High-energy protein supplements are provided to underweight children.

Study procedures

Beginning in September 2007, HIV-infected children younger than 16 years seeking HIV care were eligible for enrollment into a cohort study. Written informed consent was obtained from parents or

guardians and assent was obtained from children 8-16 years of age. Children were evaluated at study visits approximately every three months, at which time a questionnaire was administered, the child was examined and a blood specimen was obtained. At each visit CD4+ T-cell counts and percentages were measured using the Guava Easy CD4 system (Guava Technologies, Inc., Hayward, CA). During each physical examination, height and weight were measured. For children who missed study visits, home visits were attempted to ascertain their status. Information recorded before study enrollment was abstracted from medical records. The study was approved by the Ministry of Health in Zambia, the Research Ethics Committee of the University of Zambia and the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health.

For the present analysis, all children enrolled in the study and receiving ART between September 2007 and September 2009 were included. The study sample included children already receiving ART at enrollment and children initiating ART during the study period.

Statistical analysis

Data were entered in duplicate using EpiInfo (Centers for Disease Control and Prevention) and analyses were conducted in STATA, version 9 (StataCorp LP, College Station, Texas). Weight-for-age z-scores (WAZ) among children younger than 10 years of age and height-for- age (HAZ) z-scores among all children were calculated based on the WHO growth standards [25], and children with z-scores below -2 were defined as underweight and stunted, respectively. Severe immunodeficiency was defined by CD4+ T-cell percentage according to the WHO 2006 treatment guidelines [24].

WAZ and HAZ after ART initiation were assessed among children with at least one post-ART measure. Children were followed until they died, were lost to follow-up, or were administratively censored on September 30, 2009. Children who had not returned for at least 6 months were assumed lost to follow-up. For reporting outcomes at specific time points after ART initiation, measurements were aggregated to within 45 days. Treatment outcomes were evaluated using linear mixed effects models with random intercept, exchangeable correlation structure and robust standard error estimation. As changes in WAZ were not linear, a spline term was added at 7.5 months, the upper window around the 6- month measure. Covariates of interest included sex, orphan status, education of the primary caregiver, age, underweight, stunting and severe immunodeficiency at ART initiation. Covariates found to be ($p < 0.10$) or known to be associated with either outcome were included in the models. Differences in trajectories of WAZ and HAZ were assessed by each covariate of interest.

Results

Characteristics of the study population at study enrollment and ART initiation

Between September 2007 and 2009, 193 children received ART, with 67 entering the study already receiving ART and 126 initiating ART after study enrollment. Children receiving ART at study enrollment entered a median of 8.3 months (IQR: 2.3, 17.7) after initiating ART, while treatment-naïve children initiated ART a median of 2.0 months (IQR: 0.9, 6.0) after study enrollment. The median follow-up time in the study was 13.1 months (IQR: 5.1, 20.0).

Table 1. Characteristics at study enrollment and ART initiation of HIV-infected children receiving antiretroviral therapy

	Total (n=193)	Children receiving ART at study enrollment (n=67)	Children starting ART during study period (n=126)	p-value
Study enrollment				
Median age in years (IQR)	3.01 (1.62, 6.89)	4.25 (2.46, 8.61)	2.53 (1.27, 6.34)	0.0005
<1 yr	24 (12.4)	2 (3.0)	22 (17.5)	
1-1.9 yrs	38 (19.7)	8 (11.9)	30 (23.8)	
2-4.9 yrs	66 (34.2)	29 (43.3)	37 (29.4)	
5+ yrs	65 (33.7)	28 (41.8)	37 (29.4)	0.002
Male sex	99 (51.3)	43 (64.2)	56 (44.4)	0.009
Mother received PMTCT (%)	5 (2.6)	0 (0.0)	5 (4.0)	0.24
Vital status of parents (%)				
Both alive	135 (71.1)	39 (60.9)	96 (76.2)	
One parent died	37 (19.5)	15 (23.4)	22 (17.5)	
Both died	18 (9.5)	10 (15.6)	8 (6.4)	0.05
Primary caregiver (%)				
Mother/father	148 (77.5)	48 (73.9)	100 (79.4)	
Grandparent	26 (13.6)	11 (16.9)	15 (11.9)	
Aunt/uncle	12 (6.3)	5 (7.7)	7 (5.6)	
Other	5 (2.6)	1 (1.5)	4 (3.2)	0.55
Education of primary caregiver (%)				
None	11 (6.3)	3 (5.3)	8 (6.8)	
Primary	100 (57.1)	31 (54.4)	69 (58.5)	
Secondary	62 (35.4)	23 (40.4)	39 (33.1)	
Higher	2 (1.1)	0 (0.0)	2 (1.7)	0.62
ART initiation				
Median age in years (IQR)	2.93 (1.66, 6.84)	3.07 (1.71, 7.91)	2.87 (1.60, 6.73)	0.33
<1 yr	23 (11.9)	6 (9.0)	17 (13.5)	
1-1.9 yrs	41 (21.2)	15 (22.4)	26 (20.6)	
2-4.9 yrs	64 (33.2)	21 (31.3)	43 (34.1)	
5+ yrs	65 (33.7)	25 (37.3)	40 (31.8)	0.72
Median WAZ (IQR)[a]	-2.30 (-3.46, -1.37)	-2.55 (-3.92, -1.80)	-2.10 (-3.22, -1.26)	0.02
Underweight	89 (58.9)	34 (70.8)	55 (53.4)	0.04
Median HAZ (IQR)	-3.49 (-4.47, -2.41)	-4.86 (-6.26, -3.15)	-3.40 (-4.32, -2.33)	0.17
Stunted	53 (79.1)	7 (87.5)	46 (78.0)	0.53
Median CD4% (IQR)	16.3 (11.5, 20.1)	13.6 (9.7, 16.6)	17.4 (12.9, 20.5)	0.01
Severe immunodeficiency (%)[b]	95 (59.8)	26 (70.3)	69 (56.7)	0.14

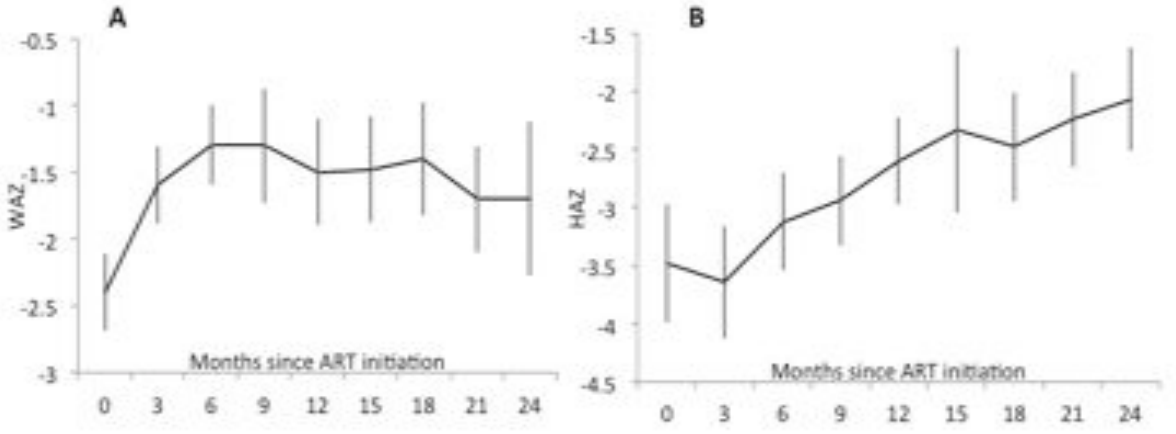
[a]among children <10 years of age.
[b]defined by age according to the 2006 WHO guidelines.

The median age was 3.0 years (IQR: 1.6, 6.9) at study enrollment and 51.3% were male (Table 1). The majority of children were cared for by a parent (77.5%) or grandparent (13.6%). Sixty-three percent of primary care- givers had no high school education and 9.5% of children were double orphans. Very few mothers (2.6%) had received drugs to prevent mother-to-child transmission.

The median age at ART initiation was 2.9 years (IQR: 1.7, 6.8). The median WAZ and HAZ at ART initiation were -2.3 (IQR: -3.5, -1.4; 58.9% underweight) and -3.2 (IQR: -4.3, -1.9; 71.9% stunted), respectively. The median CD4+ T-cell percentage at ART initiation was 16.3% (IQR: 11.5, 20.1; 59.8% severe immunodeficiency). Children who entered the study already receiving ART were significantly older and more likely to be male. In addition, they were significantly more likely to be underweight and have a lower CD4+ T-cell percentage at ART initiation.

The initial ART regimen was D4T/3TC/NVP for 40.5% of children. Other regimens included AZT/3TC/EFV (24.3%), D4T/3TC/EFV (18.9%), and AZT/3TC/NVP (13.5%). An additional three children received a regimen including ABC (2.0%) and one child received a regimen including emtricitabine and tenofovir (0.5%).

Children on ART experienced good immunologic recovery, with median CD4+ T-cell percentage increasing to 28.9% (IQR: 22.6, 37.2), 32.4% (IQR: 25.1, 39.1), and 34.2% (IQR: 30.6, 38.7) 6, 12 and 24 months after ART initiation, respectively.



	0	3	6	12	18	24
N	119	88	73	51	34	20
Mean	-2.4	-1.6	-1.3	-1.5	-1.4	-1.7
Mean change *	—	0.6	0.8	1.0	1.5	1.1
% underweight	59.7	34.1	28.8	35.3	26.5	45.0

	0	3	6	12	18	24
N	74	95	82	60	43	28
Mean	-3.5	-3.6	-3.1	-2.6	-2.5	-2.1
Mean change *	—	0.4	1.0	1.3	—	—
% stunted	71.6	79.0	80.5	66.7	60.5	46.4

Figure 1: Mean (95% CI) weight-for-age (A) and height-for-age (B) z-scores by time since ART initiation.
*sample sizes are smaller due to missing data at ART initiation.

Weight-for-age z-scores after ART initiation

For WAZ, 128 children younger than 10 years were included in the analysis, of whom 4 (3.1%) died and 4 (3.1%) were lost to follow-up after ART initiation. WAZ increased during the first 6 months of treatment and then stabilized. Mean WAZ increased from -2.4 at treatment initiation to -1.3, -1.5, -1.4 and -1.7 at 6, 12, 18 and 24 months on ART, respectively (Figure 1A). Consequently, the proportion of underweight children decreased from 59.7% at treatment initiation to 28.8%, 35.3%, 26.5% and 45.0% at 6, 12, 18, and 24 months on ART, respectively. Results of the crude longitudinal models indicated that WAZ increased by 0.12 units per month in the first 6 months of ART, and remained stable thereafter (Table 2).

Table 2. Results of the longitudinal data analysis for WAZ and HAZ after ART initiation

	***Weight for age z-scores*[a]**		***Height for age z-scores***	
	Coefficient (SE)	**p-value / p-value interaction**	**Coefficient (SE)**	**p-value / p-value interaction**
Crude model				
Time (per month) on ART			0.053 (0.012)	<0.0001
0-6 months	0.12 (0.02)	<0.0001		
>6 months	-0.003 (0.012)	0.81		
Adjusted model				
Time (per month) on ART			0.10 (0.01)	<0.0001
0-6 months	0.12 (0.02)	<0.0001		
>6 months	0.003 (0.01)	0.72		
Female	0.48 (0.21)	0.02	0.60 (0.29)	0.04
Severe immunodeficiency[b,c]	-0.35 (0.21)	0.09	-0.55 (0.29)	0.06
Age (years)[c]				
2-4.9	-0.55 (0.26)	0.04	0.49 (0.41)	0.23
≥5	-0.52 (0.27)	0.05	1.16 (0.36)	0.001
Double orphan[c]	-0.70 (0.29)	0.02		
Underweight[c]			-1.68 (0.31)	<0.0001
Stratified by WAZ at ART initiation[d]:				
WAZ ≥-2 (ref)				
0-6 months (per month)	0.04 (0.02)	0.08		
>6 months (per month)	0.04 (0.01)	0.005		
WAZ <-2 (underweight)				
0-6 months (per month)	0.19 (0.03)	<0.0001 /		
>6 months (per month)	-0.01 (0.01)	0.21 / 0.003		
Stratified by age (years) at ART initiation[d]:				
0-1.9 (ref): time (per month)			0.15 (0.025)	<0.0001
2-4.9: time (per month)			0.11 (0.020)	<0.0001 / 0.18
≥5: time (per month)			0.049 (0.014)	<0.0001 / <0.0001

[a]among children <10 years of age.
[b]defined by age according to WHO 2006 guidelines.
[c]measured at ART initiation
[d]WAZ model adjusted for sex, double orphan status, severe immunodeficiency and age at ART initiation; HAZ model adjusted for sex, severe immunodeficiency and underweight at ART initiation
severe immunodeficiency and underweight at ART initiation.

Male sex, double orphan status and older age at ART initiation were significantly associated with lower WAZ. Severe immunodeficiency at ART initiation was marginally associated with lower WAZ. Differing patterns of improvement were found only by WAZ at ART initiation, with underweight children experiencing greater increases in WAZ in the first 6 months of ART.

Height-for-age z-scores after ART initiation

For HAZ, 152 children were included in the analysis, of whom 4 (2.6%) died and 4 (2.6%) were lost to follow-up after ART initiation. A linear increase in HAZ was observed throughout treatment and mean HAZ increased from -3.5 at treatment initiation to -3.1, -2.6, -2.5, and -2.1 at 6, 12, 18 and 24 months on ART, respectively (Figure 1B). Consequently the proportion of stunted children decreased from 71.6% at treatment initiation to 80.5%, 66.7%, 60.5%, and 46.4% at 6, 12, 18 and 24 months on ART, respectively. Results of the crude longitudinal model indicated that HAZ increased by 0.053 units per month after ART initiation (Table 2).

Underweight children at ART initiation had significantly lower HAZ, while older children and females had significantly higher HAZ throughout treatment. Severe immunodeficiency at ART initiation was marginally associated with lower HAZ. Significant differences in the trajectories of HAZ were found only by age at ART initiation, with children older than 5 years at initiation experiencing significantly smaller increases in HAZ per month compared to children younger than 2 years of age.

Discussion

In this study of young HIV-infected children in rural Zambia with good immunologic recovery on ART, both weight and height-for-age improved after initiation of ART. Age and undernutrition at ART initiation impacted both WAZ and HAZ, and differences in the trajectories of WAZ and HAZ were associated with undernutrition and age at ART initiation, respectively.

Improvements in WAZ and HAZ among HIV-infected children treated with ART were found in other studies throughout sub-Saharan Africa [7-18]. The trajectories for WAZ and HAZ after ART initiation, however, differed in this study. WAZ improved for the first 6 months and then stabilized with only minimal improvements thereafter, whereas HAZ consistently improved over time. Similar trajectories for WAZ and HAZ were reported in one study in South Africa [10], while other studies found linear improvements in WAZ during the first 24 months of treatment [11,26]. Reasons for these differences are unknown but may be due to the higher levels of undernutrition observed in this rural population [26]. Over half of the study population was underweight and three-quarters stunted at ART initiation. Differences in trajectories were found between children who were underweight and those with normal weight, with greater weight improvements in the first 6 months for children underweight at ART initiation. A more consistent increase was found for children with normal weight. Consequently, it is possible that this group of rural children experienced different trajectories than the urban populations in previous studies.

Due to the relatively young age of the study population, the impact of age at ART initiation on both WAZ and HAZ could be evaluated. Older age was associated with both WAZ and HAZ at ART initiation; however, only age impacted the trajectories for HAZ, with children older than 5 years experiencing less improvement. In other studies, HAZ did not consistently improve, with some

studies finding no significant increases [12,13,17]. Discrepancies in HAZ may be due to the different age compositions of the study populations, as many studies were conducted among children with an average age older than 5 years [21]. As more infants and young children are diagnosed and started on ART, further evaluation of HAZ over time will be needed.

This study was limited by the small sample size beyond two years on ART, and the small number of children with measures available at ART initiation (Figure 1). The role of food supplementation in achieving weight and height gains in this study is unknown, as the criteria used for eligibility were not consistent across clinic staff and children did not receive supplements at every visit. In addition, no information was collected on the child's diet or on comorbidities and therefore the contribution of these factors to growth could not be assessed.

Conclusions

This study demonstrated that rural Zambian children experienced significant improvements in both weight and height after starting ART. However, even after two years of ART approximately 25% and 50% of children remained underweight and stunted, higher than observed among HIV-negative children in the same region [27]. Consequently, successful treatment with ART was not able to fully reverse the effects of HIV on growth. Partnerships between HIV treatment and nutrition programs should be explored so that children receive an integrated care and treatment approach that includes nutritional support. Further evaluation of the impact of food supplementation on growth after ART initiation is needed.

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Choolwe 2006-2007

Luyando 2007-2008

Alex 2007 – 2008

Chipego 2006 – 2009

Moono 2007 – 2008

Melitah 2006 – 2008

Innocent 1997 – 2007

Ruth 2005 – 2007

Sibajene 2005 – 2008

Memory 2002 – 2012

Susan 1999 – 2008

Prudence 2005 – 2008

Nchimunya 2006 – 2008

Chipo 2005 – 2007

Purity 2006 – 2008

Lushomo 2007 – 2008

Mainzi 2007 – 2008

Sunday 2003 – 2008

Develop 2007 – 2008

Michelo 1996 – 2008

Lukondo 2005 – 2008

Mutinta 2007 – 2010

Patricia 2007 – 2009

Orient 2008 – 2008

Bornwell 1993 – 2008

Obvious 2012-2012

Trust 2007 – 2008

Mike 2008 – 2008

Modern 2008 – 2009

Talent 2007 – 2010

Trywell 2008 – 2009

Justin 2007 – 2009

Praise 2007 – 2009

Chimuka 2008 – 2009

Kelvin 2007 – 2010

Loveness 2009 – 2009

Essential 2007 – 2009

Brian 2009 – 2009

Melody 2008 – 2010

Future 1995 – 2010

Temba 2009 - 2011

Michelo 2008 - 2009

Wisdom 2008 – 2009

Morgan 1997 – 2009

Chipo 2008 – 2010

Lweendo 2010-2011

Rejoice 2008 – 2009

Assent 2008 – 2009

Godfrey 2009 – 2009

Junior 2008 -2010

Twalumba 2010-2012

Prince 2008 – 2010

Moses 2005 - 2012

Nelson 2008- 2010

Noel 2009 - 2010

Gift 2009-2011

Tendai 1995 - 2010

Charity 2008 - 2010

Felister 2009 - 2010

Moses 2008 - 2010

Shelly 2007 - 2010

Mercy 2009- 2010

Kelvin 2010-2010

Paul 2007 - 2010

Esther 2007-2012

Happy 2009 - 2010

Grace 2009 – 2009

Even 2009 - 2011

Elvis 2008 -2011

Sandra 2003-2012

Mary 2009 - 2011

Lucky 2005 - 2010

Staywell 2008-2011

Doubt 2009 - 2011

Lister 2006 - 2012

Clilve 2005 - 2011

Ireen 2008 - 2010

Rose 2011-2012

Names were changed for confidentiality reasons

Part Four: Aspects of service delivery

Chapter 7

Risk Factors for Pre-Treatment Mortality among HIV-Infected Children in Rural Zambia: A Cohort Study

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Abstract

Background: Many HIV-infected children in sub-Saharan Africa enter care at a late stage of disease. As preparation of the child and family for antiretroviral therapy (ART) can take several clinic visits, some children die prior to ART initiation. This study was undertaken to determine mortality rates and clinical predictors of mortality during the period prior to ART initiation.

Methods: A prospective cohort study of HIV-infected treatment-naïve children was conducted between September 2007 and September 2010 at the HIV clinic at Macha Hospital in rural Southern Province, Zambia. HIV-infected children younger than 16 years of age who were treatment-naïve at study enrollment were eligible for analysis. Mortality rates prior to ART initiation were calculated and risk factors for mortality were evaluated.

Results: 351 children were included in the study, of whom 210 (59.8%) were eligible for ART at study enrollment. Among children ineligible for ART at enrollment, 6 children died (mortality rate: 0.33; 95% CI: 0.15, 0.74). Among children eligible at enrollment, 21 children died before initiation of ART and their mortality rate (2.73 per 100 person-years; 95% CI: 1.78, 4.18) was significantly higher than among children ineligible for ART (incidence rate ratio: 8.20; 95% CI: 3.20, 24.83). In both groups, mortality was highest in the first three months of follow-up. Factors associated with mortality included younger age, anemia and lower weight-for-age z-score at study enrollment.

Conclusions: These results underscore the need to increase efforts to identify HIV-infected children at an earlier age and stage of disease progression so they can enroll in HIV care and treatment programs prior to becoming eligible for ART and these deaths can be prevented.

Introduction

Since 2003, antiretroviral treatment (ART) programs in sub-Saharan Africa have rapidly scaled-up and currently provide treatment to an estimated 356,000 HIV-infected children [1]. Reports from programs indicate that treatment outcomes among children are comparable to those observed in resource-rich settings [2]. However, many children enter care at a late stage of disease progression, such that mortality rates during the first few months of treatment are high [2]. The period between enrollment into care and treatment initiation can extend for several months as eligible children and their families are prepared for the burden and challenges of ART [3]. This process can involve several clinic and home visits, psychological assessments, ART literacy training, adherence counselling, and identification of a family member or friend to provide support ('medicine companion' or 'treatment supporter') [4,5,6,7]. During this time, children also are diagnosed and treated for any concurrent opportunistic infections. In addition, children not eligible for ART at enrollment are monitored, typically every three months, and may experience rapid disease progression. Few programs report outcomes during this period prior to ART initiation, but several studies among adults [5,7,8,9,10,11] and children [3,6,12,13] indicate that significant mortality occurs among both ART eligible and ineligible individuals during this time of preparation and evaluation. This study was undertaken to determine mortality rates and identify clinical predictors of mortality during the period prior to ART initiation among both eligible and ineligible children enrolled in an ART program in rural Zambia.

Methods

Ethics Statement

The study was approved by the Government of Zambia Ministry of Health, the Research Ethics Committee of the University of Zambia and the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health. Written informed consent was obtained from parents or guardians and assent was obtained from children 8–16 years of age.

Study Population

The study was conducted at Macha Hospital in a rural area of Southern Province, Zambia. The study setting and population have been described in detail elsewhere [14,15]. Briefly, Macha Hospital is a district-level referral hospital administered by the Zambian Brethren in Christ Church. Since 2005, Macha Hospital has provided care to over 7000 HIV-infected adults and children through the Government of Zambia's antiretroviral treatment program, with additional support from the President's Emergency Plan for AIDS Relief (PEPFAR) through the non-governmental organization, AidsRelief.

Children with a positive HIV serologic test are referred to the clinic from voluntary counseling and testing programs, outpatient clinics and rural health centers. Early infant diagnosis based on detection of HIV DNA has been available since February 2008.

Clinical care is provided without charge by medical doctors and clinical officers, and adherence counseling by nurses and trained counselors. Routine follow up occurs approximately every three months. ART is initiated according to WHO guidelines at the discretion of the doctors and clinical officers. At enrollment in the clinic, children and their caregivers must attend two group counseling

sessions to avoid early attrition. Before ART initiation an individual treatment preparation counseling session is provided, and children must demonstrate their ability to adhere to non-ART medications, including multivitamins and cotrimoxazole, over two visits through self-report and pill counts. In addition, individuals must identify a family member or friend to serve as a treatment supporter.

Study Procedures

Beginning in September 2007, HIV-infected children younger than 16 years seeking HIV care were eligible for enrollment into a cohort study. Children were evaluated at study visits approximately every three months, at which time a questionnaire was administered, the child was examined and a blood specimen was obtained. The study questionnaire was designed to collect information on demographics, the vital status and education of the parents and primary caregiver, the child's medical, medication, and vaccination history, disclosure of HIV status and transportation to the clinic. During each physical examination, height and weight were measured. As part of routine clinical care, CD4+ T cell counts and percentages were measured using the Guava Easy CD4 system (Guava Technologies, Inc., Hayward,CA). Hemoglobin was measured using an ABX Micros ES 60 Hematology Analyzer (Horiba Medical, France). For children who missed study visits, home visits were attempted to ascertain their status. For children who died, cause of death was ascertained through verbal autopsy or through hospital or clinic records. Information recorded before study enrollment was abstracted from medical records.

Statistical Analysis

For the present analysis, all treatment-naïve children enrolled in the study between September 2007 and September 2010 were included. Children were followed until the first of either ART initiation, death, loss to follow-up or September 1, 2010. Children whose last visit occurred more than six months prior to September 1, 2010 were considered lost to follow-up.

Eligibility for ART at study enrollment was defined retrospectively based on the WHO criteria in effect at the time of study enrollment. At the beginning of the study, the 2006 WHO treatment guidelines were in effect [16], which recommended ART for all children with WHO stage 3 or 4 irrespective of immunologic status. For children with WHO stage 1 or 2, ART was recommended on the basis of immunologic status (≤11 months: <25%; 12–35 months: <20%; ≥36 months: 15%). Treatment guidelines were revised in 2008 [17], and ART was recommended for all children younger than 12 months of age. For children older than 12 months, ART initiation was based on clinical (WHO stage 3 or 4) and immunologic (WHO stage 1 or 2 and <20% for children 12–59 months or <15% for children ≥5 years of age) status. The 2008 WHO treatment guidelines were assumed to take effect in June, 2008. For children missing WHO stage or CD4+ T-cell percentage at enrollment, ART eligibility was defined based on immunologic or clinical criteria alone. Immunologic and clinical parameters from within three months of study enrollment were used to determine ART eligibility and clinical and immunologic status at study enrollment. Weight-for-age z-scores were calculated based on the WHO growth standards [18] and children with z-scores below -2 and -3 were defined as underweight and severely underweight, respectively.

Severe immunodeficiency was defined as CD4+ T-cell percentage by age for all children according to the 2006 WHO treatment guidelines (≤11 months: <25%; 12–35 months: <20%; 36–59 months: <15%; ≥5 years: <15%) [16]. Severe anemia was defined as hemoglobin <8 g/dL [19]. A measure of socioeconomic status (SES) was calculated based on the Demographic and Health Survey SES scale used in Zambia [20]. SES percentiles were based on the predetermined cutoffs (<25th = 0–6; 26–

50th = 7–12; 51–75th = 13–18; >75th = 19–24). Kaplan-Meier survival methods were used to estimate the cumulative probability of ART initiation and death. Survival curves were compared between groups using the logrank test. Mortality rates were calculated per 100 person-years at risk and were compared using Poisson regression. Risk factors for mortality were evaluated using Cox proportional hazards regression. Characteristics associated with mortality in univariable analysis ($p<0.1$) were considered for inclusion in the multivariable model. All analyses were conducted in SAS for Windows version 9.2 (SAS Institute Inc., Cary, NC) and Stata, version 11 (StataCorp LP, College Station, Texas).

Results

During the study period, 363 treatment-naïve HIV-infected children were invited to participate and 362 were enrolled. Three hundred and fifty-one (97%) children had sufficient information to determine their eligibility for ART and were included in the analysis. Children were enrolled in the clinic for a median of 0.20 months (interquartile range [IQR]: 0, 4.16) prior to study enrollment, and the median follow-up time in the study was 3.44 months (IQR: 0.92, 9.44). At study enrollment, the median age was 2.6 years (IQR: 1.4, 5.7), 45.1% of children were male, and 23.5% of children were single or double orphans (Table 1). Over half (54.0%) of children were moderately (24.1%) or severely underweight (30.0%) and the majority had severe disease: 40.3% had severe immunodeficiency, 51.5% were classified as WHO stage 3 or 4, and 59.8% were eligible for ART.

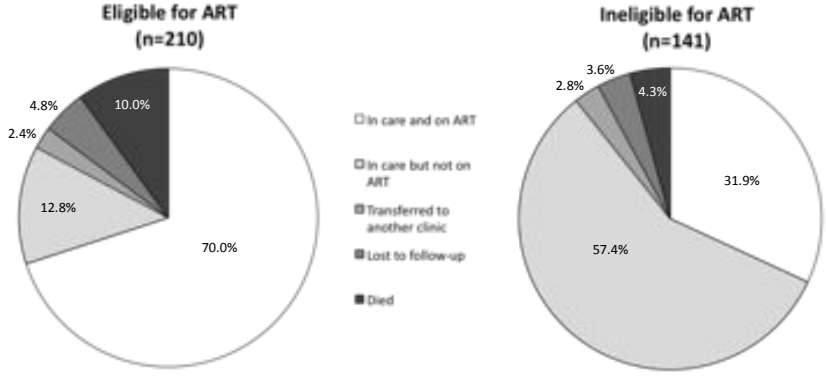

Figure 1. Outcomes at the end of the study period, by eligibility status at study enrollment.

Table 1. Baseline characteristics of treatment-naïve, HIV-infected children receiving care at Macha Hospital, Zambia from 2007-2010

	Study population (n=351) N (%)
Median age in years (IQR)(n=351)	2.6 (1.4, 5.7)
<2 yrs	140 (39.9)
2-4 yrs	109 (31.1)
≥5 yrs	102 (29.1)
Male sex (n=351)	158 (45.0)
Mother received PMTCT (n=348)	22 (6.3)
Vital status of parents (n=347)	
Both alive	264 (76.1)
One parent died	64 (18.4)
Both died	19 (5.5)
Primary caregiver (n=348)	
Mother/Father	272 (78.2)
Grandparent	39 (11.2)
Aunt/uncle	26 (7.5)
Other	11 (3.2)
Education of primary caregiver (n=337)	
None	12 (3.6)
Primary	211 (62.6)
Secondary	110 (32.6)
Higher	4 (1.2)
Socioeconomic status (n=348)	
≤25th percentile	233 (67.0)
26-50th percentile	96 (27.6)
51-75th percentile	17 (4.9)
76-100th percentile	2 (0.6)
Median WAZ (IQR)[a] (n=283)	-2.2 (-3.4, -1.3)
≥-2	133 (45.9)
< -2 to -3	70 (24.1)
< -3	87 (30.0)
Median CD4% (IQR) (n=320)	20.7 (14.7, 27.6)
Severe immunodeficiency[b]	129 (40.3)
WHO stage (n=264)	
1	50 (18.9)
2	78 (29.6)
3 or 4	136 (51.5)
Eligible for ART[c] (n=351)	210 (59.8)

[a] Among children < 10 years of age

[b] Defined by age for all children according to the 2006 WHO guidelines.

[c] Defined retrospectively according to the WHO treatment guidelines in effect at the time of study enrolment.

By the end of the study period, 192 (54.7%) children started ART, 15 (4.3%) were lost to follow-up, 9 (2.6%) transferred to another clinic, 27 (7.7%) died, and 108 (30.8%) were still in care but not receiving ART. Children eligible for ART at enrollment were significantly more likely to have started ART ($p<0.0001$) and died ($p = 0.05$) (Figure 1). Among children eligible at enrollment, the median time from study enrollment to ART initiation was 2.07 months (IQR: 0.92, 6.59) (Figure 2).

At 12 and 24 months, the cumulative probability of ART initiation was 84.1% and 88.0%, respectively. Chart reviews were conducted for 69 children who had either taken more than three months to initiate ART or had been enrolled in the study for more than three months without starting ART to determine reasons for potential delays in ART initiation (Table 2). The majority of children (81.2%) were found to have an identifiable reason for delay. The most common reason was delay on the part of the family (33.9%), due to poor adherence of the child to other medications, family unpreparedness to adhere to the more frequent clinic visit schedule or the child missing clinic visits.

Table 2. Evaluation of delays in ART initiation among 69 children eligible for ART at enrolment who had either taken more than three months to initiate ART or had been enrolled in the study for more than 3 months without starting ART.

	N (%)
Delayed ART initiation	**56 (81.2)**
Family delay	**19 (33.9)**
Poor adherence	3 (5.4)
Family unpreparedness[a]	4 (7.1)
Family unpreparedness and poor adherence	8 (14.3)
Child stopped coming to the clinic	4 (7.1)
Provider delay	**16 (28.6)**
Misinterpretation of laboratory results, HIV staging or eligibility criteria by clinician	10 (17.9)
Other	6 (10.7)
Medical delay	**11 (19.6)**
Hepatitis or elevated ALT	1 (1.8)
Tuberculosis	10 (17.9)
Combined family, provider or medical delay	**9 (16.1)**
Provider and family delay	6 (10.7)
Tuberculosis and poor adherence	2 (3.6)
Tuberculosis and family unpreparedness	1 (1.8)
Unknown	**1 (1.8)**
No delay	**13 (18.8)**
Eligible by WHO stage only[b]	10 (76.9)
Other	3 (23.1)
Total	**69 (100.0)**

[a]Family unpreparedness included refusal to come at shorter intervals and problems with transportation.
[b]Children who are underweight or have specific symptoms and opportunistic infections (e.g. prolonged diarrhea) are classified as WHO stage 3 at that visit. However, they are not considered eligible for ART if their weight or symptoms improve with treatment at subsequent visits.

Other reasons included provider delay (28.6%), primarily due to misinterpretation of laboratory results, HIV staging or eligibility criteria by clinicians; medical delay (19.6%), primarily due to treatment for tuberculosis; and a combination of family, provider and medical delays (16.1%). Among children ineligible at enrollment, the cumulative probability of ART initiation at 12 and 24 months was 35.3% and 41.0%, respectively (Figure 2).

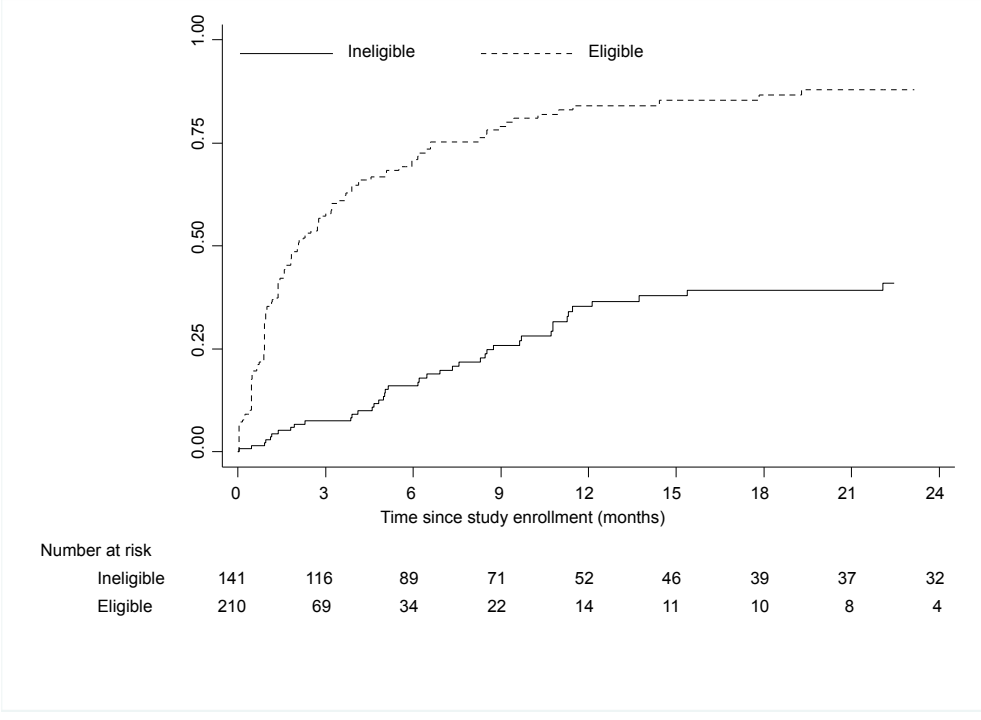

Figure 2. Cumulative probability of ART initiation by eligibility status at study enrollment.

Among the 27 children who died, the median time from study enrollment to death was 1.90 months (IQR: 0.36, 3.41). Factors contributing to death were available for 25 children and included pneumonia (n = 10), tuberculosis (n = 10), undernutrition (n = 10), diarrhea (n = 8), cerebral malaria (n = 1), meningitis (n = 2), renal failure (n = 1), hepatitis (n = 1) and measles (n = 1). Place of death was available for 21 children; 16 (76.2%) children died in the hospital and 5 (23.8%) children died at home. The cumulative probabilities of death by 6, 12 and 24 months after study enrollment were 9.9% (18.6% eligible, 3.2% ineligible), 12.0% (18.6% eligible, 6.1% ineligible), and 13.4% (24.4% eligible, 6.1% ineligible; logrank test = 0.0003; Figure 3), respectively.

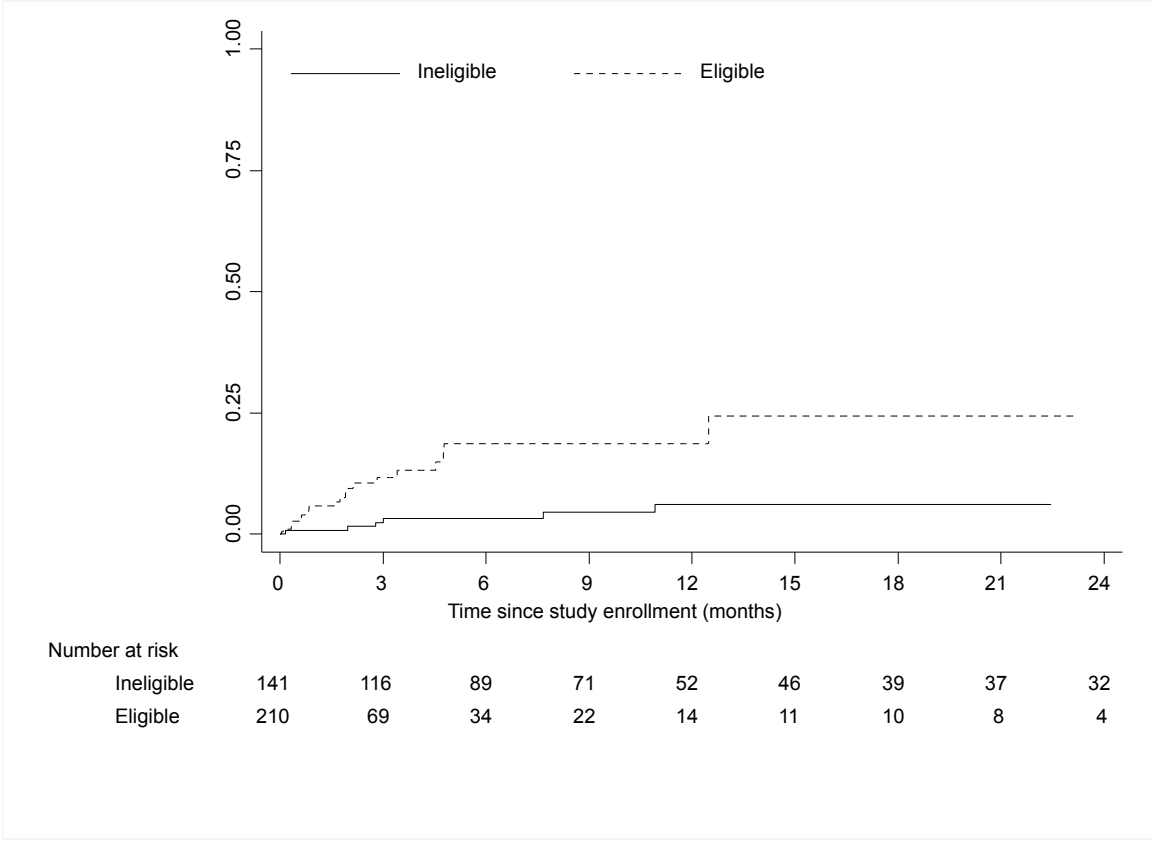

Figure 3. Cumulative probability of mortality by eligibility status at study enrollment.

The overall pre-ART mortality rate was 1.05 (95% CI: 0.72, 1.53) per 100 person-years. Among children ineligible for ART, the mortality rate was 0.33 (95% CI: 0.15, 0.74) per 100 person-years. Among children eligible for ART, the mortality rate was 2.73 (95% CI: 1.78, 4.18) per 100 person-years and was significantly higher than among children ineligible for ART (incidence rate ratio: 8.20; 95% CI: 3.20, 24.83). The mortality rate was highest in the first three months after study enrollment at 2.58 per 100 person-years (95% CI: 1.65, 4.05), and was higher among children eligible for ART (eligible: 4.50; 95% CI: 2.75, 7.34; ineligible: 0.79; 95% CI: 0.25, 2.44; incidence rate ratio: 5.70; 95% CI: 1.63, 30.55). Twenty-one (77.8%) of the children who died were eligible for ART at study enrollment, and this group was therefore more similar in characteristics at study enrollment to the surviving children eligible for ART (Table 3).

Table 3. Comparison of characteristics at study enrollment between children who died, and children who were eligible and ineligible for ART at study enrollment.

	Children who died (n=27) N (%)	Surviving children eligible for ART[a] (n=189) N (%)	p-value[b]	Surviving children ineligible for ART[a] (n=135) N (%)	p-value[b]
Male sex	10 (37.0)	87 (46.0)	0.38	61 (45.2)	0.44
Median age (IQR)	1.4 (0.7, 2.6)	2.0 (1.1, 4.7)	0.07	4.3 (2.1, 7.0)	<0.0001
<2 yrs	18 (66.7)	94 (46.8)		31 (23.0)	
2-4 yrs	5 (18.5)	58 (28.9)		49 (36.3)	
≥5 yrs	4 (14.8)	49 (24.4)	0.20	55 (40.7)	<0.0001
Median WAZ (IQR)[c]	-3.7 (-4.4, -2.1)	-2.3 (-3.6, -1.4)	0.03	-1.8 (-2.6, -0.9)	0.0002
≥-2	4 (21.1)	71 (42.0)		59 (54.6)	
< -2 to -3	4 (21.1)	37 (21.9)		31 (28.7)	
< -3	11 (57.9)	61 (36.1)	0.12	18 (16.7)	0.0003
Median CD4% (IQR)	20.7 (14.9, 26.8)	17.0 (10.5, 21.1)	0.03	25.8 (22.1, 33.3)	0.001
Severe immunodeficiency[d]	10 (41.7)	119 (67.2)	0.01	0 (0.0)	<0.0001
Median hemoglobin (IQR)	8.9 (7.7, 9.3)	9.5 (8.6, 10.5)	0.002	10.6 (9.3, 11.3)	<0.0001
<8 g/dL	8 (33.3)	21 (11.4)	0.001	7 (5.9)	<0.0001
WHO stage					
1	1 (5.3)	11 (7.1)		38 (41.3)	
2	3 (15.8)	21 (13.7)		54 (58.7)	
3 or 4	15 (78.9)	121 (79.1)	0.51	0 (0.0)	<0.0001
Parent's vital status					
Both alive	19 (73.1)	151 (79.9)		94 (71.2)	
One parent died	7 (26.9)	28 (14.8)		29 (22.0)	
Both died	0 (0.0)	10 (5.3)	0.18	9 (6.8)	0.36

[a]ART eligibility defined retrospectively according to the WHO treatment guidelines in effect at the time of study enrollment.
[b]p-value comparing surviving children to children who died.
[c]Among children <10 years of age.
[d]Defined by age according to the 2006 WHO guidelines

Among children eligible for ART at study enrollment, age, WAZ score and anemia were associated with mortality in the crude analysis and were further evaluated. In multivariable analysis, lower WAZ score (HR for < -3 vs. ≥ -2: 7.63; 95% CI: 1.80, 32.39) and anemia (HR: 3.50; 95% CI: 1.25, 9.77) remained independently associated with a higher risk of mortality (Table 4). Younger age was marginally independently associated with mortality (hazard rate [HR] for <2 years vs. ≥5 years: 3.58; 95% CI: 0.98, 13.09). CD4+ T-cell percentage at study enrollment and sex were not associated with mortality. The cumulative probability of mortality six months after study enrollment was 8.0% for children with WAZ ≥ -2, 24.3% for children with WAZ -3 to -2, and 35.0% for children with WAZ < -3 (logrank test =0.04; Figure 4A). The cumulative probability of mortality six months after enrollment was 13.8% for children without anemia and 34.6% for children with anemia (logrank test= 0.001; Figure 4B). The cumulative probability of mortality six months after enrollment was 33.7% for children younger than 2 years of age, 4.5% for children 2 to 4 years of age, and 9.2% for children 5 years of age or older (logrank test = 0.01; Figure 4C). Similar risk factors were found among children who were ineligible for ART at study enrollment, although the number of children and deaths were small and precluded a full evaluation (Table 4).

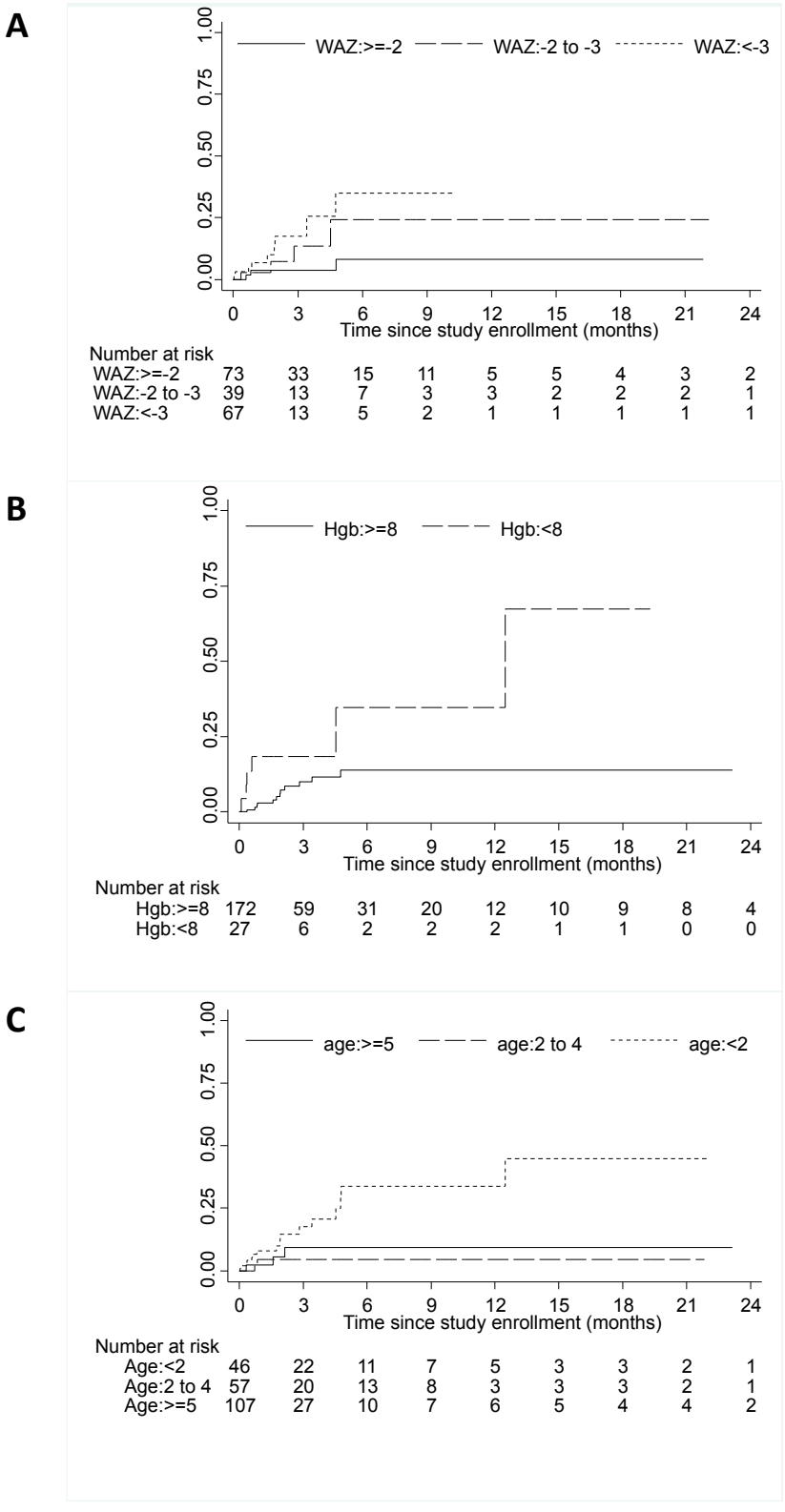

Figure 4. Cumulative probability of mortality by WAZ (A), haemoglobin level (B), and age (C) at study enrolment among children eligible for ART.

Table 4. Risk factors for mortality among children eligible and ineligible for ART at study enrolment.			
	Children eligible for ART (n=210; 21 deaths)		**Children ineligible for ART (n=141; 6 deaths)**
	Crude HR (95% CI)	**Adjusted HR (95% CI)**	**Crude HR (95% CI)**
Male sex	0.53 (0.20, 1.37)	---	2.47 (0.45, 13.49)
Age (years)			
<2	3.31 (0.96, 11.42)	3.58 (0.98, 13.09)	3.90 (0.35, 43.23)
2-4	0.63 (0.11, 3.78)	1.03 (0.16, 6.60)	3.29 (0.34, 31.74)
≥5	1	1	1
Weight-for-age z-score[a]	0.74 (0.54, 1.01)		0.48 (0.26, 0.91)
≥ -2	1	1	---
< -2 to -3	2.76 (0.62, 12.34)	4.47 (0.88, 22.74)	---
< -3	4.62 (1.23, 17.28)	7.63 (1.80, 32.39)	---
CD4% (per 10)	1.17 (0.71, 1.95)	---	0.53 (0.16, 1.75)
Severe immunodeficiency[b]	0.92 (0.36, 2.36)	---	---
Hemoglobin <8 g/dL	2.54 (1.48, 4.36)	3.50 (1.25, 9.77)	6.84 (1.25, 37.40)

[a]Among children < 10 years of age.
[b]Defined by age according to the 2006 WHO guidelines

Discussion

Mortality among HIV-infected children in the period prior to ART initiation was high, particularly in the first few months after enrollment among children eligible for ART. Risk factors for mortality included younger age, undernutrition and anemia, and were similar among children eligible and ineligible for ART at study enrollment.

Most treatment programs report on mortality and treatment outcomes after initiation of ART and few have focused on the period prior to ART initiation. However, this period should be evaluated along with the interval after ART initiation as it provides additional insight into the population of children reached by the program and the effectiveness of the treatment program in reducing mortality. A study of HIV-infected children from Cambodia evaluated mortality prior to and after ART initiation and found that the majority of deaths occurred before starting ART [6]. Similar to this study, the majority of deaths occurred within the first three months after enrollment and among children who were eligible for ART. The overall mortality rate for children who never started ART was 7.7 per 100 person-years and was higher than the mortality rate among children receiving ART (2.0 per 100 person-years). Another study among 192 Ugandan children who were ineligible for ART found that 19% progressed to a WHO stage 3 or 4 event, death or ART eligibility after a median of 605 days [13]. Most events, three of which were deaths, occurred within the first year of follow-up. Predictors of progression included lower CD4+ T-cell percentage, higher viral load, and younger age. Anemia was marginally associated with progression but WAZ was not associated. Additional studies reported that 1% of eligible and 3% of ineligible children in Zambia died prior to ART initiation [3], and that 12.3% of ART-naïve children compared to 9.5% of children on ART in Mozambique died during follow-up [12]. Similar trends of high pre-ART mortality in the first few months of follow-up and similar risk factors were also found in studies of HIV-infected adults [5,7,8,9,10]. In this study, the cumulative mortality prior to ART initiation was 13.3% and was comparable to the cumulative

mortality of 14.4% among children initiating ART in this cohort [15]. In addition, the mortality rate in the first three months after study enrollment among children eligible for ART was comparable to the mortality rate in the first three months after ART initiation (unpublished data). While mortality rates differ between programs depending on the characteristics of the population and the rigor of ascertainment of deaths, these estimates indicate that a significant proportion of children entering care are dying before they initiate ART.

The majority of deaths occurred in the first few months after study enrollment and during the period of preparation for ART. The median time to ART initiation among eligible children was 2.1 months. Other studies reported an average time of 4.7 months to ART initiation among children in Cambodia [6], 0.9 months among children in Lusaka, Zambia [3], one month among adults in South Africa [7], and 4.3 months among adults in The Gambia [11]. This period of preparation takes several clinic or home visits to ensure caregivers are prepared to administer life-long medication and be responsible for maintaining high adherence in their children. This process can take longer in rural areas as transportation and travel distance pose challenges, and necessitate longer intervals between visits and synchronization of visits with other family members [3]. Additional delays in ART initiation can lengthen this period, and can be due to treatment for concurrent tuberculosis or other illnesses, insufficient human resources (primarily in the early years of a treatment program), incorrect clinical or immunological staging by physicians, and social problems in the family, such as lack of transportation, food insecurity, no legal guardian, history of suboptimal adherence, lack of disclosure of child's status to another adult, denial of child's status or need for ART and ill health of the caregiver [6,21]. Similar reasons for delay were identified for 26.7% of children eligible for ART at study enrollment in this study. Many of these delays were warranted to stabilize the child's health or ensure that the family was prepared for the burden of administering ART to the child. However, some delays also were attributable to clinician judgment and could potentially be prevented through continued training.

In this study, 77.8% of children who died were eligible for ART and were therefore characterized by a younger age and later stage of disease progression, including higher WHO stage, lower CD4+ T-cell percentage, lower WAZ, and lower hemoglobin. These characteristics were well-established risk factors for mortality among HIV-infected children in sub-Saharan Africa prior to the availability of ART [22,23,24]. Many children enroll in treatment programs when eligible for ART [3], as did 60% of children in this study. Identification of risk factors for mortality that could distinguish those children at risk of early death might allow for interventions to halt disease progression and prevent death. In this study, risk factors for mortality among children eligible for ART included younger age, severe undernutrition and severe anemia. Interestingly, CD4+ T-cell percentage was not predictive of early mortality, although the median CD4+ T-cell percentage was relatively high in this group of children. These risk factors are similar to risk factors for early mortality among children receiving ART [3,25,26,27]. As a result of the late stage of disease at study enrollment, most deaths occurred within the first few months of follow-up before children could prepare for and start ART. Consequently, continued efforts are needed to promote testing of infants and children so that HIV-infected children can be identified and enrolled into care at an earlier stage of disease. If children could initiate treatment at lower levels of immunosuppression and with fewer concurrent illnesses, many of these pre- ART deaths could be prevented.

There were several limitations to this study. First, the follow-up time was relatively short and the number of observed deaths was low, particularly among children ineligible for ART, which limited our ability to evaluate risk factors for mortality in this group. Second, study enrollment was used as a proxy for clinic enrollment, as children had only been seen in the clinic for a short duration prior to study enrollment. The reported mortality rates may, therefore, underestimate the true mortality rate in this population, as deaths may have occurred soon after clinic enrolment, which would not have been captured. However, the loss to follow-up was low and it is unlikely that many deaths were not reported. The mortality rate is likely to be accurate for the group of children surviving long enough to enroll in the study. Lastly, eligibility at study enrollment was defined retrospectively based on immunologic and clinical criteria. Some misclassification of eligibility status is likely to have occurred, as children with undernutrition in this setting who are initially classified as WHO stage 3 or 4 are not considered eligible for ART if they gain weight on nutritional support and treatment. In addition, some children were missing information on WHO stage or CD4+ T-cell percentage at study enrollment and were classified based on immunologic or clinical criteria alone.

In summary, a significant number of HIV-infected children enrolled in treatment programs die before initiating ART as a result of late-stage disease. These results further underscore the need to increase efforts to identify HIV-infected children at an earlier age and stage of disease so they can enroll in HIV care and treatment programs prior to becoming eligible for ART. In this way, they and their family can be prepared to initiate life-long therapy and receive the full benefits of treatment.

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Chapter 8

Effectiveness of efavirenz-based regimens in young HIV-infected children treated for tuberculosis: a treatment option for resource-limited settings

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Abstract

Background: Antiretroviral treatment (ART) options for young children co-infected with HIV and tuberculosis are limited in resource-poor settings due to limited data on the use of efavirenz (EFV). Using available pharmacokinetic data, an EFV dosing schedule was developed for young co-infected children and implemented as the standard of care at Macha Hospital in Southern Province, Zambia. Treatment outcomes in children younger than 3 years of age or weighing less than 10 kg receiving either EFV-based ART plus anti-tuberculous treatment or nevirapine-based (NVP) ART were compared.

Methods: Treatment outcomes were measured in a cohort of HIV-infected children seeking care at Macha Hospital in rural Zambia from 2007 to 2010. Information on the diagnosis and treatment of tuberculosis was abstracted from medical records.

Results: Forty-five children treated for tuberculosis initiated an EFV-based regimen and 69 children initiated a NVP-based regimen, 7 of whom also were treated for tuberculosis. Children receiving both regimens were comparable in age, but children receiving EFV started ART with a lower $CD4^+$ T-cell percentage and weight-for-age z-score. Children receiving EFV experienced increases in both $CD4^+$ T-cell percentage and weight-for-age z-score during follow-up, such that levels were comparable to children receiving NVP after two years of ART. Cumulative survival after 12 months of ART did not differ between groups (NVP:87%; EFV:80%; p=0.25). Eleven children experienced virologic failure during follow-up. The adjusted hazard ratio of virologic failure comparing EFV to NVP was 0.25 (95% CI: 0.05,1.24) and 0.13 (95% CI: 0.03,0.62) using thresholds of 5000 and 400 copies/mL, respectively. Five children receiving EFV were reported to have had convulsions after ART initiation compared to only one child receiving NVP (p=0.04).

Conclusion: Despite poorer health at ART initiation, children treated for tuberculosis and receiving EFV-based regimens showed significant improvements comparable to children receiving NVP-based regimens. EFV-based regimens should be considered for young HIV-infected children co-infected with tuberculosis in resource-limited settings.

Introduction

The dual burden of human immunodeficiency virus (HIV) infection and tuberculosis represents a significant threat to the health of children in sub-Saharan Africa. An estimated 3.4 million children worldwide are infected with HIV [1], the majority of whom live in sub-Saharan Africa. In areas of high HIV prevalence, as many as half of incident pediatric tuberculosis cases occur in children infected with HIV [2]. Tuberculosis is among the most common causes of persistent lung disease in HIV-infected children older than 3 years [3], is one of the leading causes of death from respiratory illness in HIV-infected children [4], and accelerates HIV disease progression [5].

Because of the poor prognosis in young children infected with HIV and tuberculosis, there is no alternative to concurrent treatment of both infections [6]. Simultaneous initiation of both therapies increases the risk of immune reconstitution syndrome, but extensive delays in starting antiretroviral therapy (ART) should be avoided. Current WHO recommendations for co-infected children are that ART should be initiated 2-8 weeks after starting treatment for tuberculosis [6], and a cohort study suggested that ART should not be delayed more than 60 days [7].

The optimal antiretroviral regimen for children receiving anti-tuberculous treatment has not been established. Rifampicin is a potent inducer of the cytochrome P450 system and hepatic glucuronidation, resulting in significant reductions in serum levels of several antiretroviral drugs [8]. The alternative, rifabutin, has fewer drug interactions but is often not available in most resource-limited settings, has not undergone formal pharmacokinetic and safety studies in children, and is associated with corneal deposits and other ocular toxicity in children [9]. The preferred antiretroviral regimen for co-administration with rifampicin in adults and older children is two nucleoside reverse transcriptase inhibitors (NRTI) plus efavirenz (EFV). For children younger than 3 years of age receiving rifampicin, current WHO recommendations for antiretroviral therapy include two NRTI plus nevirapine (NVP) or three NRTI [6]. However, both of these options are problematic and have been associated with reduced virologic efficacy compared to other regimens [10,11,12,13].
The product labeling for EFV includes dosages only for children older than 3 years of age and weighing greater than 10 kg, as EFV dosing for younger or smaller children had not been established. The 2006 [14] and 2008 [15] WHO recommendations followed the weight-band dosing table in product labeling (approximately 15 mg/kg/day). However, EFV clearance is not linearly proportional to weight and data are emerging that higher dosages may be required in children older than 3 years of age [16,17,18,19]. Children younger than 3 years of age may require even higher relative dosages. In the P1021 trial, which assessed the efficacy of a once-daily regimen containing didanosine, emtricitabine and EFV, serum EFV levels in children younger than 3 years of age were within the therapeutic range when given a fixed dosage of 390 mg (median 47 mg/kg) [20,21], significantly higher than current recommendations. In the P1070 study, a non-linear weight band dosing scheme averaging approximately 40 mg/kg was used in African and Asian children younger than 3 years of age. Drug levels in the target range were achieved in the majority of children, except those with the slow-metabolizer CYP2B6 516 TT genotype who had higher drug levels [22].

Given the limited antiretroviral treatment options in resource-constrained settings for children receiving rifampicin, and the need to initiate ART as soon as possible to avoid excess morbidity and

mortality, an EFV dosing schedule extrapolated from available data was developed for the clinical care of young children with tuberculosis. We assessed the effectiveness of EFV-based regimens by comparing treatment outcomes between young co-infected children receiving both anti-tuberculous therapy and EFV-based ART regimens and young children with and without tuberculosis receiving NVP-based ART regimens enrolled in an observational cohort study.

Methods

Ethics Statement

The study was approved by the Ministry of Health of the Government of Zambia, the Research Ethics Committee of the University of Zambia and the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health. Written informed consent was obtained from parents or guardians and assent was obtained from children 8-16 years of age.

Setting and clinical care

The study was conducted at the pediatric HIV clinic at Macha Hospital in rural Southern Province, Zambia. The study setting and population were described in detail elsewhere [23,24]. Briefly, Macha Hospital is a district-level referral hospital that has provided care to over 7500 HIV-infected adults and children since 2005. HIV care services, including antiretroviral treatment, are provided through the Government of Zambia's antiretroviral treatment program, with support from the President's Emergency Plan for AIDS Relief (PEPFAR) through the non-governmental organization, AIDSRelief. Care and treatment are provided free of charge by medical doctors and clinical officers. Mothers and infants are provided drugs to prevent mother to child transmission (PMTCT) according to WHO guidelines [25]. Children diagnosed with HIV infection are determined to be eligible for ART according to the WHO treatment guidelines [6,14,15]. Standard ART regimens consist of stavudine or zidovudine plus lamivudine, and a non-nucleoside reverse transcriptase inhibitor (NVP or EFV).

Young children suspected of having tuberculosis undergo a physical examination and chest radiograph. The clinical diagnosis of tuberculosis is based on the results of these examinations and the judgment of the health care provider. Children with tuberculosis are treated with isoniazid (6 months), rifampicin (6 months), and pyrazinamide (2 months). Children treated with rifampicin and eligible for ART are treated with two NRTI and EFV. An EFV dosing schedule based on available data [16,17,18,19,20,21,26] was provided to clinics supported by AIDSRelief throughout Zambia beginning in 2006 and adopted as the standard of care at Macha Hospital for young children with tuberculosis. The schedule included a fixed dosage of 300 mg daily (using scored 600 mg tablets) for children weighing between 4 and 20 kg.

Young children without tuberculosis and eligible for ART were treated with two NRTI and NVP. NVP was dosed using the WHO 2006 dosing recommendations, which included guidance on induction and maintenance dosing [14].

Study procedures

Beginning September 2007, HIV-infected children younger than 16 years of age and seeking care at the pediatric HIV clinic at Macha Hospital were eligible for enrollment into an observational cohort study. This report describes a subset of these subjects. Children were evaluated at study visits

approximately every three months, at which time a questionnaire was administered to obtain information on demographics, household characteristics and medical history. The child was examined to measure height and weight, and a blood specimen was obtained to measure $CD4^+$ T-cell counts and percentages (Guava Easy CD4 system; Guava Technologics, Inc., Hayward, CA) and ALT (Reflotron Plus Chemistry Analyzer and Cobas C111; Roche Molecular Systems) as part of clinical care. Plasma levels of HIV RNA were quantified by reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor v. 1.5, Roche Molecular Systems; lower limit of detection of 400 copies/mL) as part of the study. For children receiving ART, adherence was assessed by pill counts and syrup volume measurements. For children who missed study visits, home visits were attempted to ascertain their status.

Information regarding prior and current diagnosis and treatment of tuberculosis and adverse events while receiving ART were abstracted from medical records. Adverse events were defined as any clinical sign or symptom or elevated ALT measure possibly or probably related to ART. Elevated ALT measures were graded according to WHO guidelines [6].

Study population

This analysis was restricted to children younger than 3 years of age or weighing less than 10 kg who were enrolled in the observational cohort study and initiated ART with a regimen consisting of two nucleoside analogues plus either EFV or NVP prior to January 1, 2011 (Figure 1). The group of children receiving EFV consisted solely of those receiving concurrent treatment for HIV and tuberculosis. The group of children receiving NVP included children with and without tuberculosis. The children with tuberculosis were inadvertently initiated on a regimen containing NVP and were switched to EFV at the discretion of the clinic physician or clinical officer. Children initiating ART with NVP who were subsequently diagnosed with tuberculosis (n=4) were excluded. Children were categorized as receiving an EFV or NVP-based regimen according to their regimen at initiation or during follow-up.

Study outcomes, including mortality, virologic failure, $CD4^+$ T-cell percentage, growth and adherence were assessed until May 1, 2011. Children were included in the analysis until they died, were lost to follow-up or were administratively censored on May 1, 2011. Children whose last study visit occurred more than six months prior to May 1, 2011 were considered lost to follow-up.

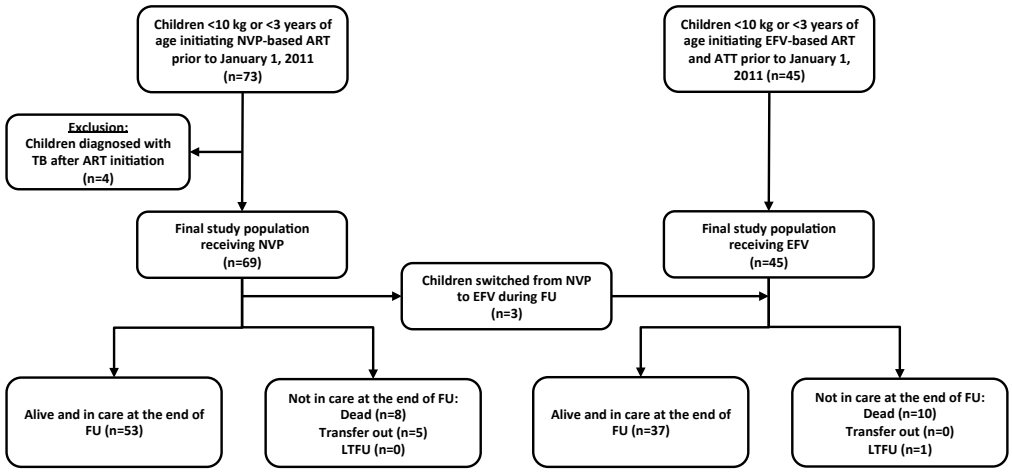


Figure 1. Study Flowchart

Statistical analysis

Data were entered in duplicate using EpiInfo (Centers for Disease Control and Prevention) and analyses were conducted using SAS for Windows version 9.1 (SAS Institute Inc., Cary, NC) and STATA, version 9 (StataCorp LP, College Station, TX). Characteristics of children receiving NVP and EFV at ART initiation were compared using chi-square tests for binary variables and Wilcoxon rank sum tests for continuous variables. Severe immunosuppression was defined by age according to the 2006 WHO treatment guidelines [14]. Weight-for-age (WAZ) z-scores were calculated based on WHO growth standards [27], and children with WAZ below -2 were considered underweight. Children with hemoglobin <8 g/dL were considered severely anemic [28]. Use of drugs by the mother or child to prevent mother to child transmission (PMTCT) was ascertained by interview and confirmed by review of medical records. If measurements were not available from the visit at which ART was initiated, results within 3 months prior to the date of initiation were used.

Clinical and immunologic outcomes were evaluated among children with at least one measurement after ART initiation using longitudinal data analysis. Linear mixed effects models with random intercept, exchangeable correlation structure and robust standard error estimation were used. Interaction terms between EFV and time were included to determine whether trajectories of the outcomes differed between children receiving EFV or NVP. For $CD4^+$ T-cell percentage, a spline term was added at 6 months as trajectories were not linear over time.

Survival after ART initiation was evaluated using Kaplan Meier survival curves. Survival curves for children receiving NPV and EFV were compared using the log-rank test. EFV, the primary exposure of

interest, was treated as a time-varying covariate as three children who initiated ART with NVP and were receiving anti-tuberculous therapy at ART initiation subsequently switched to EFV. Cox proportional hazards models were used to compare the risk of death between children receiving NVP and EFV.

Virologic outcomes also were evaluated. The proportion of children with viral suppression, defined as a viral load below the limit of detection (400 copies/mL), was calculated for each visit after ART initiation and compared between children receiving NPV and EFV using chi-square tests. As for mortality, virologic failure was evaluated using Kaplan Meier survival curves and Cox proportional hazards models with EFV treated as a time-varying covariate. Virologic failure was defined according to WHO guidelines [6] as at least two viral load measurements >5000 copies/mL among children who received at least six months of ART, and was defined on the date of the second measurement. An alternate definition of virologic failure was also assessed using a cut-off of ≥400 copies/mL. Children entered the analysis on their first viral load measure at or beyond 6 months of ART and were included until they experienced virologic failure, were lost to follow-up or were administratively censored on May 1, 2011.

For all analyses, characteristics known to be associated with the outcome from the published literature or found to be associated with the outcome ($p<0.10$) in the crude models were considered for inclusion in the multivariable models.

Caregivers were instructed to bring all unused medications at each visit and adherence was measured by pill count or measurement of liquids for each drug prescribed. Adherence measures were capped at 100%. For children taking more than one drug, the adherence percentage of the drug to which the patient was least adherent was used. Children were defined as adherent using two thresholds, depending upon whether they took more than 90% or 95% of drugs prescribed. The proportion of children receiving NVP or EFV who were adherent at each visit and at all visits was compared using chi-square tests.

Results

Characteristics of the study population

Between September 2007 and December 2010, 114 children younger than 3 years of age or weighing less than 10 kg initiated antiretroviral treatment and were eligible for analysis, including 45 children receiving an EFV-based regimen and 69 children receiving a NVP -based regimen.

Among children receiving EFV, the median time between the start of anti-tuberculous therapy and initiation of ART was 1.9 months (IQR: 1.0, 2.4; range 0.6-5.4). Twenty-eight (62%) children started ART during the intensive phase of anti-tuberculous therapy (within the first two months), and 17 (38%) during the continuation phase (within 2-6 months; median 2.4 months). Among children receiving NVP, five children were previously treated for tuberculosis but started ART after completion of anti-tuberculous therapy. Seven children receiving NVP were also receiving anti-tuberculous therapy at ART initiation (three initiated ART during the intensive phase and four during the continuation phase) and three subsequently switched to EFV (time to switch: 0.4, 0.9, and 1.3 months after ART initiation).

The median age at ART initiation was 17.4 months for children receiving EFV and 20.2 months for children receiving NVP, and the majority of children were female (Table 1). Few children receiving

either EFV or NVP had previous exposure to antiretroviral drugs as part of the PMTCT program and the majority of children received an ART backbone of stavudine and lamivudine. Children receiving EFV were significantly more likely to be classified as WHO stage 3 or 4, and have a lower $CD4^+$ T-cell percentage, weight and WAZ. They were marginally more likely to have a lower hemoglobin level (Table 1).

At the end of follow-up, 8 (12.1%) children receiving NVP and 10 (20.8%) receiving EFV died (p=0.21), and 5 (7.6%) children receiving NVP and one (2.1%) receiving EFV transferred to another clinic (p=0.19). No child was lost to follow-up. The median duration of follow-up on ART was comparable between groups, with 13.4 months (IQR: 5.9, 27.0) of follow-up for children receiving NVP and 16.7 months (IQR: 8.2, 23.3) for children receiving EFV (p=0.68).

Table 1. Characteristics of children receiving nevirapine and efavirenz at ART initiation

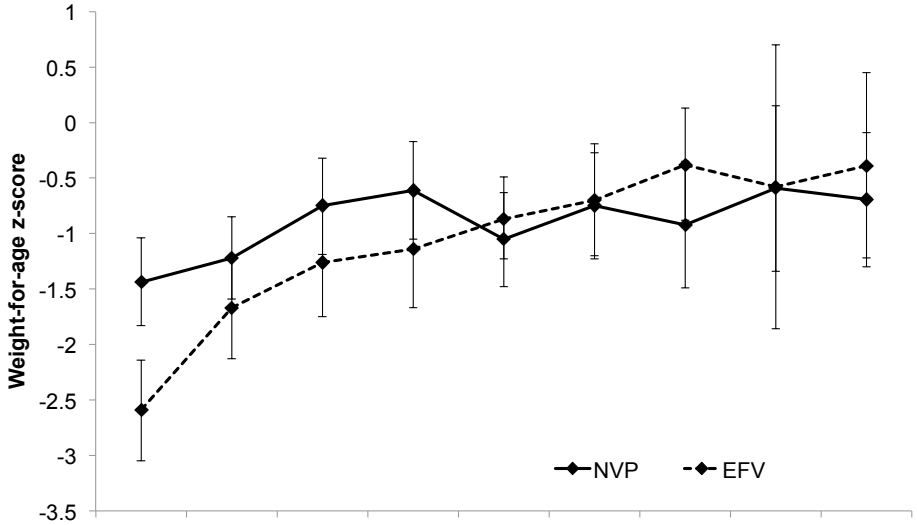
	N (NVP/EFV)	Children receiving NVP	Children receiving EFV	p-value
Age in months: median (IQR)	69/45	20.2 (11.0, 27.1)	17.4 (13.6, 22.6)	0.36
Male: n (%)	69/45	31 (44.9)	17 (37.8)	0.45
Mother and/or child received drugs to prevent mother-to-child transmission of HIV (confirmed or self-reported): n (%)	69/45	6 (8.7)	6 (13.3)	0.21
WHO stage 3 or 4: n (%)	32/36	25 (78.1)	36 (100.0)	0.01
CD4%: median (IQR)	64/41	18.5 (15.7, 25.2)	14.2 (9.8, 20.7)	0.007
Severe immunosuppression[a]: n (%)		41 (64.1)	29 (70.7)	0.48
Hemoglobin (g/dL): median (IQR)	66/44	9.4 (8.6, 10.3)	9.0 (7.9, 9.8)	0.08
Weight (kg): median (IQR)	69/45	8.8 (7.2, 10.0)	7.2 (6.2, 8.6)	0.005
Weight-for-age z-score: median (IQR)	69/45	-1.7 (-2.8, -0.5)	-2.7 (-3.6, -1.8)	0.001
Underweight[b]: n (%)		32 (46.4)	31 (68.9)	0.02
BCG vaccination scar present: n (%)	69/45	65 (94.2)	41 (91.1)	0.53
Regimen: n (%)	69/45			
Stavudine/lamivudine		59 (85.5)	33 (73.3)	
Zidovudine/lamivudine		9 (13.0)	10 (22.2)	
Abacavir/lamivudine		1 (1.5)	2 (4.4)	0.25

[a] Severe immunosuppression defined by age according to the 2006 WHO treatment guidelines

[b] Underweight defined as weight-for-age z-score less than -2

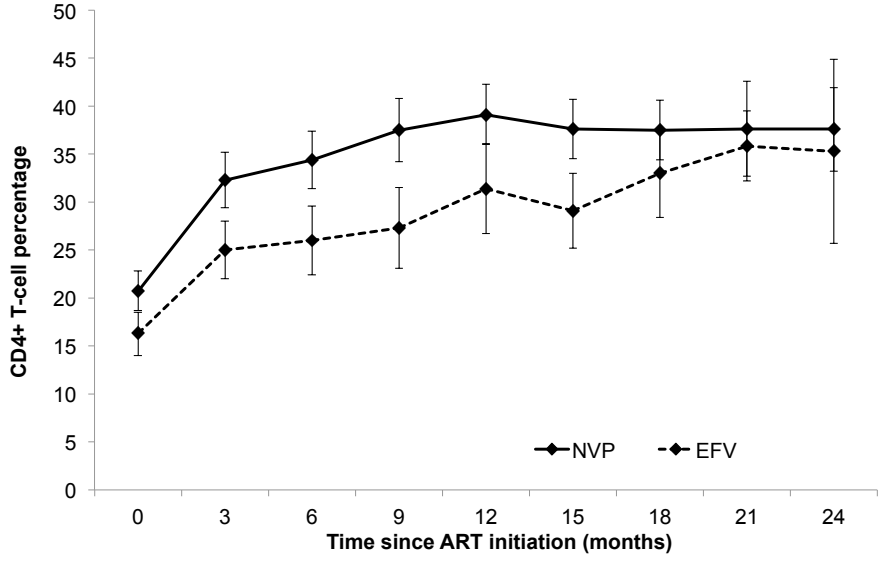
Clinical and immunologic outcomes

Children receiving EFV initiated ART with a significantly lower WAZ than children receiving NVP, and experienced significantly greater increases in WAZ during follow-up (NVP: mean change +0.1, standard deviation [SD] 1.0; EFV: +1.8, SD 1.6, at 12 months; p<0.0001) (Figure 2). Results of the longitudinal data analysis showed significantly different trajectories of WAZ between the two groups of children, with children receiving EFV experiencing a significantly greater increase in WAZ per month, such that they were able to catch-up to children receiving NVP within two years of ART (Table 2).



NVP	N:	58	53	44	34	35	30	26	22	19
	Mean:	-1.4	-1.2	-0.8	-0.6	-1.1	-0.7	-0.9	-0.6	-0.7
EFV	N:	39	38	34	32	28	22	18	17	8
	Mean:	-2.6	-1.7	-1.3	-1.1	-0.9	-0.7	-0.4	-0.6	-0.4

Figure 2. Mean weight-for-age z-score (95% confidence interval) after ART initiation by regimen



NVP	N:	55	39	40	29	29	27	22	20	16
	Mean:	20.7	32.3	34.4	37.5	39.1	37.6	37.5	37.6	37.6
EFV	N:	37	34	28	25	24	19	15	14	5
	Mean:	16.3	25.0	26.0	27.3	31.4	29.1	33.0	35.8	35.3

Figure 3. Mean CD4+ T cell percentage (95% confidence interval) after ART initiation by regimen

Children receiving EFV also initiated ART with a significantly lower $CD4^+$ T-cell percentage than children receiving NVP, but experienced comparable increases in $CD4^+$ T-cell percentage during follow-up (NVP: +16.9%, SD 8.4; EFV: +15.0%, SD 9.6 at 12 months; p=0.47) (Figure 3). Results of the longitudinal data analyses showed significantly different trajectories of $CD4^+$ T-cell percentages between the two groups of children. Among children receiving NVP, $CD4^+$ T-cell percentage increased rapidly in the first 6 months of ART and then stabilized for the duration of follow-up (Table 2). In contrast, among children receiving EFV, $CD4^+$ T-cell percentage increased more slowly in the first 6 months but continued to increase for the duration of follow-up, such that levels were comparable among all children after two years of ART (Table 2).

Virologic failure

Within the first 3 months of ART, the majority of children receiving NVP (80.7%) and EFV (87.5%; p=0.50) achieved virologic suppression. The majority of children maintained virologic suppression at 12 (NVP: 78.8%; EFV: 91.7%; p=0.19) and 24 months (NVP: 68.4%; EFV: 77.8%; p=0.61) of ART. Virologic failure was assessed among the 72 children (40 receiving NVP and 32 receiving EFV) with at least two viral load measures at or beyond 6 months of ART. Four children receiving EFV (12.5%) and 7 children receiving NVP (17.5%; p=0.56) experienced virologic failure (Figure 4; log-rank test: p=0.63; Table S1). None of the children receiving NVP who experienced virologic failure were also receiving anti-tuberculous therapy at ART initiation. The risk of virologic failure was not significantly different among children receiving EFV compared to children receiving NVP (hazard ratio [HR]: 0.73; 95% CI: 0.21, 2.49). After adjusting for $CD4^+$ T-cell percentage and WAZ at ART initiation, receipt of PMTCT, and number of viral load measures, the risk of virologic failure was lower among children receiving EFV (adjusted HR: 0.25; 95% CI: 0.05, 1.24; Table 3), although this result was not statistically significant. When virologic failure was defined by two viral load measures above the lower limit of detection (400 copies/mL) after 6 months of ART, the percentage of children with virologic failure was 15.6% among children receiving EFV compared to 22.5% among children receiving NVP (adjusted HR: 0.13; 95% CI: 0.03, 0.62; Table 3).

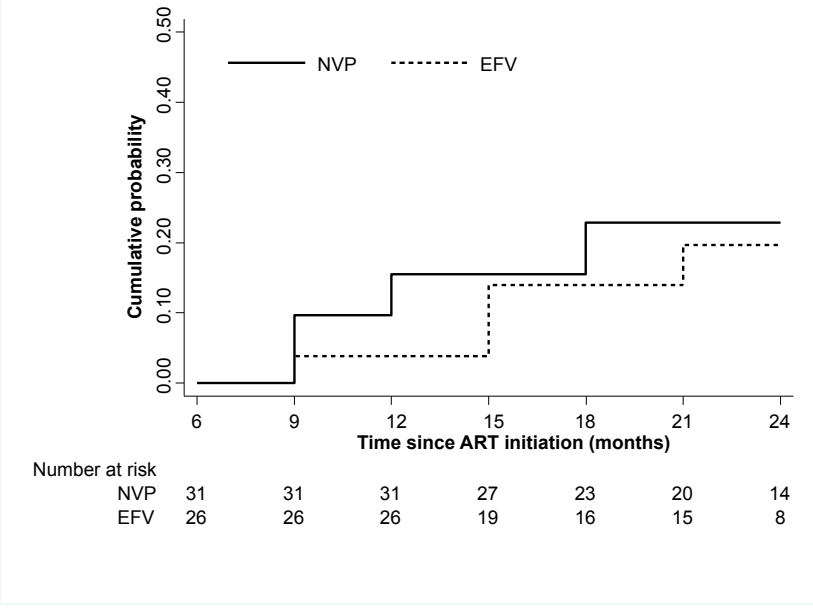


Figure 4. Cumulative probability of virologic failure after 6 months of ART by regimen

Table 2. Changes in CD4+ T-cell percentages and weight-for-age z-scores after ART initiation by regimen

	Crude			Adjusted		
	Children receiving NVP	Children receiving EFV	p-value	Children receiving NVP	Children receiving EFV	p-value
CD4+ T-cell percentage (CD4%)			[a]			[b]
CD4% at ART initiation (SE)	22.61 (1.09)	18.42 (1.08)	0.006	25.41 (1.93)	22.79 (2.01)	0.12
Increase in CD4% per month in first 6 months of ART (SE)	2.04 (0.17)	1.49 (0.21)	0.05	2.04 (0.18)	1.51 (0.21)	0.06
Increase in CD4% per month after 6 months of ART (SE)	-0.11 (0.10)	0.37 (0.10)	0.001	-0.11 (0.10)	0.36 (0.11)	0.001
Weight-for-age z-score (WAZ)			[a]			[c]
WAZ at ART initiation (SE)	-1.25 (0.17)	-2.04 (0.21)	0.005	-1.07 (0.25)	-1.41 (0.25)	0.009
Increase in WAZ per month (SE)	0.02 (0.01)	0.07 (0.02)	0.003	0.02 (0.01)	0.07 (0.02)	0.008

[a] Results shown are from linear mixed effects models with random intercept, exchangeable correlation structure and robust standard error estimation. Interaction terms between EFV and time were included to determine whether trajectories of the outcomes differed between children receiving EFV or NVP. For CD4+ T-cell percentage, a spline term was added at 6 months as trajectories were not linear over time.

[b] Adjusted for hemoglobin, weight-for-age z-score, and age at ART initiation

[c] Adjusted for hemoglobin, CD4+ T-cell percentage, weight-for-age z-score, and age at ART initiation

Table 3. Crude and Adjusted models for virologic failure

	Virologic failure threshold of 5000 copies/mL		Virologic failure threshold of 400 copies/mL	
	Crude HR (95% CI)	**Adjusted [a] HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted [a] HR (95% CI)**
EFV	0.73 (0.21, 2.49)	0.25 (0.05, 1.24)	0.72 (0.24, 2.15)	0.13 (0.03, 0.62)
CD4% at ART initiation (per 5)	0.83 (0.54, 1.28)	0.60 (0.34, 1.06)	0.76 (0.51, 1.13)	0.53 (0.31, 0.91)
WAZ at ART initiation				
≥ -2	1	1	1	1
-2.1 to -3	0.56 (0.11, 2.81)	0.56 (0.11, 2.93)	0.40 (0.08, 2.00)	0.37 (0.07, 1.95)
< -3	1.47 (0.37, 5.88)	4.21 (0.69, 25.69)	1.81 (0.55, 5.92)	7.48 (1.36, 41.01)
Receipt of PMTCT	2.05 (0.44, 9.50)	8.37 (0.90, 78.30)	1.28 (0.28, 5.91)	9.61 (1.03, 89.39)

[a] Additionally adjusted for number of viral load measure

Mortality

Eighteen deaths were recorded among study children (NVP: 12.1%; EFV: 20.8%; p=0.21). Among children who died, the median time to death after ART initiation was 1.6 months (IQR: 1.1, 4.3) among children receiving NVP and 3.4 months (IQR: 0.9, 7.3) among children receiving EFV (p=0.41). Cumulative survival was high at 6 months (NVP: 89%, 95% CI: 79, 95; EFV: 87%, 95% CI: 74, 94) and 12 months (NVP: 87%, 95% CI=76, 93; EFV: 80%, CI=65, 89) after initiating ART and did not differ significantly between groups (Figure 5; log-rank test: p=0.25). The mortality rate per 100 person-years was 8.71 (95% CI: 4.36, 17.41) among children receiving NVP and 15.81 (95% CI: 8.51, 29.38) among children receiving EFV. The risk of mortality was non-significantly higher among children receiving EFV (HR: 1.72; 95% CI: 0.68, 4.36). After adjusting for $CD4^+$ T-cell percentage, WAZ and hemoglobin at ART initiation, no difference in mortality was observed (adjusted HR: 1.00; 95% CI: 0.30, 3.31).

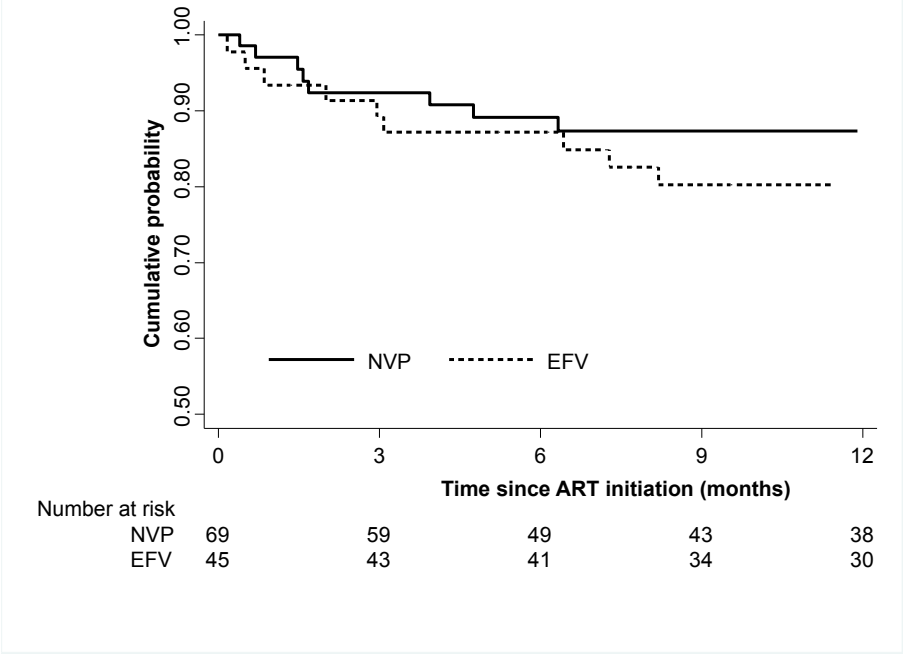


Figure 5. Cumulative survival after ART initiation by regimen

Adherence

The percentage of children who took more than 90% of their dispensed medication at all visits, verified by pill count and syrup measurement, was 56% for children receiving NVP and 46% for children receiving EFV (p=0.35). No significant differences were observed in adherence between children receiving NVP or EFV at any of the study visits (Table S2). Similar results were obtained when adherence was defined as taking more than 95% of dispensed medication.

Adverse events associated with antiretroviral therapy

None of the children discontinued EFV or NVP because of adverse events. Five children receiving EFV were reported to have had convulsions after ART initiation compared to only one child receiving NVP (p=0.04). Convulsions were reported 2 weeks to 9 months after ART initiation. No children were prescribed antiepileptic drugs. The dose of EFV was reduced in one child whose caregiver reported

intermittent seizures at one clinic visit 3 months after ART initiation. The child was reported to have had no more convulsions, was switched to NVP after completing anti-tuberculous treatment, and died in the home five months later with symptoms of gastroenteritis and pneumonia. In the other five children, including one child with convulsions reported before and after EFV initiation, three children whose convulsions were suspected to be related to febrile episodes (2 receiving EFV, 1 receiving NVP), and one child with suspected HIV encephalopathy, treatment was continued without modification and the seizures did not recur during the period of observation. No other differences in clinical symptoms were found between children receiving EFV and NVP. Twenty-two children had transiently elevated alanine aminotransferase levels (ALT ≥ 62.5 U/L [6]) during follow-up: 29.4% of children receiving NVP and 19.4% of children receiving EFV (p=0.29). The median time from ART initiation to the first episode of elevated ALT was 30 weeks (IQR: 26, 49; range 2-129) among children receiving NVP and 49 weeks (IQR: 28, 76; range: 23-76) among the children receiving EFV. All episodes were grade 1 or 2 events and no child required a change or discontinuation of treatment as a result of the elevated ALT.

Discussion

Despite poorer health at ART initiation, children younger than 3 years of age who were treated for tuberculosis and received an EFV-based ART regimen showed significant improvements in clinical, immunological and virologic outcomes, comparable to young children receiving a NVP-based regimen.

To our knowledge, no studies of the virologic efficacy of EFV-based regimens have been conducted among children younger than 3 years of age to support recommendations for its use in this population. However, use of EFV-based regimens for young children co-infected with tuberculosis would be a useful alternative treatment strategy given the limited treatment options available. WHO currently recommends that HIV-infected infants and children younger than 3 years of age and treated for tuberculosis receive either two NRTI plus NVP or three NRTI [6]. However, there are significant drawbacks to both options. When co-administered with rifampicin, studies have found NVP levels to be significantly reduced in both adults [29,30,31] and children [32,33], thereby increasing the likelihood of drug resistance and virologic failure. Increasing the dose of NVP when co-administered with rifampicin may achieve target drug levels [31,34], but may also lead to unacceptable toxicity and discontinuation rates [14,34]. There is also increasing evidence that NVP is inferior to EFV and other regimens in terms of virologic efficacy among adults and children, with [35,36] and without [11,12,13,37] tuberculosis. Regimens comprising 3 NRTI are also problematic, as they have been associated with high rates of virologic failure in both children [10] and adults [38], particularly when baseline viral loads exceed 100,000 copies RNA/mL [39,40]. In co-infected children, who are likely to have high baseline viral loads, the risk of such failure is likely to be unacceptably high.

An alternative treatment option not endorsed by the WHO for young children with tuberculosis is a regimen consisting of 2 NRTI plus ritonavir-boosted lopinavir (LPV/r). As with NVP, lopinavir levels are significantly reduced by rifampicin [8]. Doubling the dose of LPV/r to overcome this pharmacokinetic interaction has resulted in high toxicity and discontinuation rates [41], or persistently inadequate serum concentrations [42]. One small study in South African children found

that increasing the dose of ritonavir to achieve a LPV/r ratio of 1:1 resulted in acceptable pharmacokinetics for most children with little reported toxicity [43]. However, ritonavir as a single agent is not yet widely available in many resourced-limited settings and is associated with poor tolerability [44].
Consequently, there is need for alternative treatment strategies for young children with tuberculosis and data to support their use. The dosing schedule for EFV in Zambia was developed based on available pharmacokinetic data [16,17,18,19,20,21,26] and was independent of the observational cohort study. Children with tuberculosis receiving EFV-based regimens in this study achieved good clinical and immunologic outcomes that were comparable to children receiving NVP-based regimens, most of whom were not co-infected with tuberculosis. Similar to studies in adults [35,36], our findings suggest that children receiving EFV-based regimens were more likely to achieve virologic suppression compared to children receiving NVP-based regimens. Children with tuberculosis receiving EFV-based regimens had higher mortality compared to children receiving NVP-based regimens, although the difference was not statistically significant within the limited power conferred by the few number of deaths. This difference was presumably due to the poorer clinical and immunologic state of the children with tuberculosis, and was not observed after adjusting for these factors. In other studies, co-infection with tuberculosis was associated with increased mortality in children receiving ART [45].

All children tolerated EFV and, in contrast to other studies [20,46,47,48,49], no child discontinued use during the period of observation. Due to the young age of the study population, symptoms were assessed by caregiver report and many symptoms possibly related to EFV use, including loss of concentration, sleep disorders, or psychotic reactions, were difficult to evaluate. Caretakers and guardians were asked about symptoms and complaints in routine clinical care but not specifically about possible adverse events related to ART or EFV, which may have resulted in underreporting of side effects. However, if adverse events did occur and were missed by the guardian and healthcare worker, they were likely mild and transient. ALT was the only laboratory measure assessed during follow-up; however, the relevance of elevated ALT measurements is unclear as they occurred without symptoms and only sporadically in most children.
The reports by parents or caretakers of a seizure in five of the children receiving EFV and one receiving NVP are concerning but a causal association is difficult to establish in this observational study. In preclinical studies of EFV, convulsions were seen in monkeys with high EFV levels [50]. Only a single case of seizures related to EFV use in children has been reported [51] in a child who developed absence seizures in association with high levels of EFV and a slow-metabolizer genotype. All children with seizures reported here continued their drug (one with EFV dose reduction) without further report of seizures, and given the limited diagnostics available, the contribution of ART to the seizures is difficult to determine. The greater frequency of the CYP2B6 TT genotype associated with slow metabolism in Africans [52], and the median half-life of only 11.4 hours in young children that makes relatively large dosages necessary to achieve adequate trough levels, means that some children will have transient high drug levels. Shortening the dosing interval to 12 hours in small children is a potential strategy to avoid high peak levels that might lead to toxicity.

Although informative and encouraging, this study has several limitations. This was an observational cohort study and the diagnosis of tuberculosis and decisions regarding ART regimens were made by the treating clinicians. These decisions were independent of the observational cohort study from

which data for this report were abstracted, and there was no provision for pharmacokinetic studies or comprehensive safety monitoring. With the implementation of the EFV dosing schedule at the HIV clinic, children with tuberculosis were prescribed an EFV-based ART regimen. Consequently, the characteristics of the children receiving EFV-and NVP-based ART regimens were different, as the majority of children receiving NVP-based regimens were not co-infected with tuberculosis. Attempts were made to account for these differences in the analysis but measures of all potentially relevant characteristics were not available. The diagnosis of tuberculosis in children is difficult and radiographic or microbiologic tests were not performed on all children in the study. We attempted to address this issue by excluding children diagnosed with tuberculosis after ART initiation but could not account for children with undiagnosed tuberculosis during the study period. Additional limitations include the small sample size, which limited the power to detect statistically significant differences between the two groups (particularly for virologic outcomes), the relatively short duration of follow-up, and, as previously described, the difficulties in measuring EFV-related side effects.

Conclusions

This is the first study to demonstrate that EFV can be used effectively in young HIV-infected children with tuberculosis. Additional studies will be required to validate and optimize an EFV dosing strategy for young children co-infected with TB. Given the increasing number of young HIV-infected children starting ART in sub-Saharan Africa, the high burden of tuberculosis, the limited treatment options in this region, and the limited virologic efficacy of NVP, use of EFV in young children should be considered.

References

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Chapter 9

Scaling-up access to antiretroviral treatment (ART): a comparison of outcomes among HIV-infected children receiving ART at mobile and hospital-based HIV clinics in rural Zambia

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Abstract

Background: Travel time and distance are barriers to care for HIV-infected children in rural sub-Saharan Africa. Decentralization is one strategy to scale-up access to antiretroviral therapy (ART), but few such programs have been evaluated. We compared outcomes for children receiving care in mobile and hospital-based HIV clinics in rural southern Zambia.

Methods: Outcomes were measured within an ongoing cohort study of HIV-infected children seeking care at Macha Hospital, Choma District, Southern Province, Zambia since September 2007. Children in the outreach group received ART from the Macha HIV clinic and transferred to one of three mobile outreach clinics administered by Macha Hospital. Children in the hospital group received ART at the Macha HIV clinic and reported Macha Hospital as the nearest healthcare facility.

Results: 111 children transferred to the outreach clinics and 77 were included in the analysis. After transfer to the outreach clinic, travel time was significantly shorter and fewer caretakers used public transportation. Consequently, 56% of caretakers reported lower transportation costs and 67% faced fewer obstacles getting to the clinic. Caretakers reported receiving the same quality of care at the outreach clinic, although some caretakers and health care providers perceived an inferior quality of service provision at the outreach clinics. Sixty-eight children received ART at the outreach clinics and were compared to 41 children in the hospital group. At ART initiation, median age, weight-for-age z-scores (WAZ) and CD4+ T-cell percentages were similar for children in the hospital and outreach groups. Children in both groups experienced similar increases in WAZ and $CD4^+$ T-cell percentages; however, children in the outreach group were more likely to experience virologic failure (18.2% vs. 3.5%; $p=0.06$). The median percentage of visits with full adherence (>95%) was significantly lower in the outreach compared to the hospital group (69.2% vs. 79.3%; $p<0.05$).

Conclusions: Despite similar clinical and immunologic outcomes, children in the outreach group were less likely to maintain virologic suppression, potentially due to lower adherence. Continued adherence counseling is critical for the success of decentralized care for HIV-infected children in rural sub-Saharan Africa.

Introduction

In 2011, an estimated 300,000 children were newly infected with the human immunodeficiency virus (HIV) in sub-Saharan Africa, bringing the total number of children living with HIV in the region to 3.1 million [1]. Over the last decade, great progress has been made in providing these children access to lifesaving treatment. The number of children receiving antiretroviral therapy (ART) in sub-Saharan Africa increased from 85,000 in 2006 to 387,500 in 2010 [2]. However, progress must continue so all eligible HIV-infected children have access to treatment. Only 21% of children in need currently receive ART [2].

In much of sub-Saharan Africa, provision of free ART services has created huge demands on the health system that are not sustainable given current levels of infrastructure and human resources. This has necessitated a shift away from a medical model of care, primarily used in resource-rich countries and relying on highly trained medical personnel in specialized healthcare facilities to provide individualized HIV care and treatment, to a public health model that delivers treatment to more individuals [3]. The public health model relies on decentralization of HIV services to increase access, particularly in rural areas, task-shifting of activities to overcome the dearth of healthcare personnel [4], and standardized and simplified regimens and care packages to facilitate administration of care and treatment to large numbers of patients [5].

Different strategies for decentralizing HIV services have emerged in sub-Saharan African countries, adapted to local situations, influenced by varying roles of donor support, and incorporating lessons learned over the past decade. Many programs have implemented services at primary health centers, with care and treatment administered by general practitioners, clinical officers or nurses [6-20]. Several of these programs are assisted by mobile teams from hospital programs to support ART provision in primary health centers that do not have the full complement of facilities and human resources to provide comprehensive HIV services. Others have implemented home-based [21-23] and community-based [24] programs, with care and medication delivered closer to the home by trained volunteers or field officers. By delivering care and treatment closer to home, these programs have succeeded in removing the main structural barriers, including transportation and distance to the clinic, to initiating and sustaining care [25]. Evaluations of these programs, many of which have been conducted among adults, have found improved retention and lower loss to follow-up compared with centralized, hospital-based care [6-9, 17, 20].

While decentralization has succeeded in increasing access to care for large numbers of patients, particularly in rural areas, one concern is that transitioning from specialized healthcare facilities and trained healthcare personnel may compromise the quality of care. The published evaluations of treatment outcomes in decentralized programs have largely been favorable and several, but not all [6, 16], programs found similar or better survival and clinical and virologic outcomes compared with hospital-based care [7-9, 17, 20-22]. However, additional evaluations are needed of decentralized programs, particularly for children, to ensure they receive optimal care and the full benefits of treatment. In rural southern Zambia, a mobile ART program for children was evaluated and treatment outcomes were compared among HIV-infected children receiving care in mobile and hospital-based HIV clinics.

Methods

ART provision in Zambia

In 2004, the Government of Zambia initiated public sector ART programs, with roll-out beginning in primary care clinics in the Lusaka Urban District [26] and scaling up throughout the country. The program provides ART and basic laboratory tests, including CD4+ T-cell counts, free of charge. The number of ART sites increased from four in 2004 to 454 in 2010 [27],

While 61% of the Zambian population resides in rural areas [28], ART services are primarily offered in urban areas and in district level hospitals where the infrastructure and human and technical resources are greatest. To reach those affected by HIV in rural areas and increase access to HIV services, the Zambian Ministry of Health introduced the national Mobile ART Services program in 2007 [29]. Under this program, mobile ART teams of medical professionals were created at district hospitals. Rural health centers (RHC) in the catchment area were selected as designated ART outreach sites to be visited every two weeks by the mobile ART teams. Rural health centers provide reproductive, maternal and child health care, treatment for tuberculosis, HIV testing, and other basic services, but generally do not have the training or capacity to provide ART. The mobile ART team assists staff at the ART outreach site in providing ART services, builds capacity, and coordinates laboratory services. This program has contributed to the decentralization of ART services to the primary health care level to maximize limited resources and reach the greatest number of people in need.

Study setting, Clinical Care and Referral Procedures

This study was conducted at the rural HIV clinic at Macha Hospital in Southern Province, Zambia. The study setting and population have been described in detail elsewhere [30, 31]. In brief, Macha Hospital serves as a referral hospital for at least 13 rural health centers, providing services for patients within an 80 km radius. The catchment area of Macha Hospital is populated by traditional villagers living in small, scattered homesteads, characteristic of much of rural sub-Saharan Africa, with an estimated population size of over 150,000 persons. The HIV clinic has provided care to over 8500 HIV-infected adults and children since 2005. HIV care services, including antiretroviral treatment, are provided through the Government of Zambia's antiretroviral treatment program, with support from the President's Emergency Plan for AIDS Relief. The clinic provides care and treatment free of charge by physicians, clinical officers and nurses.

Children diagnosed with HIV infection are determined to be eligible for ART according to guidelines established by the Ministry of Health [32]. Children eligible for ART must undergo counseling to ensure that the family is prepared for them to initiate ART. Upon initiation, children are seen every two weeks for the first month and every month for the following two months. Thereafter, the child is seen at three-monthly intervals if adherence and clinical response are good. Standard ART regimens consist of zidovudine, stavudine or abacavir plus lamivudine, and nevirapine or efavirenz.

Due to increasing patient numbers and considerable travel distance to access HIV services [30], the HIV clinic began a mobile ART program in 2007. Three rural health centers were selected as outreach clinics based on distance and size of the catchment populations, and were located 13 km (Mapanza RHC in Choma District), 21 km (Chilala RHC in Kalomo District) and 46 km (Moobola RHC in Namwala District) from the hospital. In 2010 Chilala RHC began providing ART services independently and children who were seen in the outreach clinic were officially transferred from the Macha HIV clinic.

The selected outreach clinics are staffed with an average of one clinical officer and a minimum of two nurses. The outreach team from the Macha Hospital clinic consists of at least one clinical officer or licentiate, nurse, pharmacy dispenser, laboratory assistant, counselor and data entry clerk. Medications, medical consumables and transportation are provided by the hospital. As laboratory testing cannot be performed at the outreach clinics, blood samples are collected and transported from the outreach clinic to the Macha Hospital laboratory, and results are returned during the next outreach visit. Clinically stable patients with good adherence are provided with a 3-month supply of medication. Children are eligible for referral to the outreach clinic for care and treatment if they have been stable on ART for at least three months, demonstrated good adherence, have no opportunistic infections, and their caregiver requested to receive care closer to home. Children not yet eligible for ART and in stable condition can also be referred to the outreach clinic with the understanding that referral back to the hospital clinic might be needed once the child becomes eligible for ART or their condition worsens. Few children start ART at an outreach clinic.

Study Procedures

Beginning in September 2007, HIV-infected children younger than 16 years of age and registered at the HIV clinic at Macha Hospital were eligible for enrollment into an observational cohort study. This report describes a subset of these children.

Children were evaluated at study visits approximately every three months. At each visit, a structured questionnaire was administered to the caregiver to collect information on socio-demographics, household characteristics, and medical and treatment history. The child was examined to measure height and weight, and a blood specimen was obtained to measure $CD4^+$ T-cell counts and percentages (Guava Easy CD4 system; Guava Technologics, Inc., Hayward, CA) as part of clinical care. Plasma levels of HIV RNA were quantified by reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor v. 1.5, Roche Molecular Systems; lower limit of detection of 400 copies/mL, upper limit of detection 750,000 copies/mL) as part of the study. Adherence was assessed by pill counts and syrup volume measurements. For children who missed study visits, home visits were attempted to ascertain their status. Upon implementation of the mobile ART program, some study children were transferred to outreach clinics and a study assistant was added to the outreach team to continue study procedures at outreach visits. An additional questionnaire was administered to the caretaker during the outreach clinic visit to obtain information on health care delivery system related factors, including access to care and perceived quality of care at the outreach clinic.

Statistical analysis

Two analyses were conducted. The first analysis compared modes of transportation and travel time before and after transfer to the outreach clinic and assessed the perceived quality of care at the outreach clinics. HIV-infected children who transferred to the outreach clinic and whose caregiver completed a questionnaire both at study entry and upon transfer to the outreach clinic were eligible to be included in this analysis.

The second analysis compared treatment outcomes between children receiving ART who transferred to the outreach clinics and children receiving ART at the Macha HIV clinic who reported the Macha HIV clinic as their hospital-affiliated rural health center. This group was selected for comparison as they live in the vicinity of the clinic and would not have been transferred to an outreach clinic. Children receiving ART who were transferred to an outreach clinic before September 1, 2011 and who had a study visit after transfer were eligible for inclusion in the analysis in the outreach group.

Children receiving ART who reported the Macha HIV clinic as their rural health center, initiated ART before September 1, 2011 and had at least one study visit after ART initiation were eligible for inclusion in the analysis in the hospital group.

Children in both groups remained in the analysis until the first of death, transfer, loss to follow-up, or administrative censoring on March 1, 2012. Transfer in this context was defined as the transfer of care to a clinic other than one of the outreach clinics. Children attending Chilala Clinic when it became independent were censored on their last study visit. Loss to follow-up was defined as failure to attend a study visit for at least six months prior to March 1, 2012.

Descriptive statistics were used to compare the hospital and outreach groups on characteristics at study entry and at ART initiation. A measure of socio-economic status (SES) was calculated based on the Demographic and Health Survey SES scale used in Zambia [33], with scores ranging from 0 to 24. SES percentiles were based on the predetermined cutoffs ($<25^{th}$=0-6; $26\text{-}50^{th}$=7-12; $51\text{-}75^{th}$=13-18; $>75^{th}$=19-24). Weight-for-age z-scores (WAZ) among children younger than 10 years of age were calculated based on the WHO growth standards [34], and children with z-scores below -2 were defined as underweight. Severe immunodeficiency was defined by CD4+ T-cell percentage according to the WHO 2006 treatment guidelines [35]. If laboratory tests were not available from the visit at which ART was initiated, results were used within three months prior to the date of initiation.

Immunologic, clinical and virologic treatment outcomes were assessed, including CD4+ T-cell percentage, WAZ and virologic failure. For CD4+ T-cell percentage and WAZ, children were included if they had at least one measure available after ART initiation. To report outcomes at specific time points, measurements were aggregated to within 45 days. Both outcomes were evaluated using linear mixed effects models with random intercept, exchangeable correlation structure and robust standard error estimation. As neither outcome was linear over time, a spline term was added at 7.5 months, the upper window around the 6-month measure. The primary exposure in the models was clinic (hospital vs. outreach), which was treated as a time-varying covariate. Interactions between clinic and time were included in the models to determine whether trajectories of the outcomes differed between children in the hospital and outreach clinics. Other covariates associated ($p<0.10$) with the exposure or outcomes were included in the adjusted models.

For virologic outcomes, the proportion of children with viral suppression, defined as a HIV viral load below the limit of detection (400 copies/mL), was calculated for each visit after ART initiation. Virologic failure was defined as at least two viral load measures >400 copies/mL among children receiving at least six months of ART, and was defined on the date of the second measurement. The proportion of children with viral suppression at each visit and with virologic failure during follow-up was compared between children in the hospital and outreach groups using chi-square tests.

Adherence during follow-up was also assessed. Caregivers were instructed to bring all unused medications to each clinic visit and adherence was measured by pill count or measurement of liquids for each drug prescribed. Adherence measures were capped at 100%. For children taking more than one drug, the adherence percentage of the drug to which the patient was least adherent was used. Full adherence was defined as taking more than 95% of drugs prescribed. The proportions of children who were adherent at each visit and at all visits were compared between children in the hospital and outreach clinics using chi-square tests.

All analyses were conducted using SAS for Windows version 9.1 (SAS Institute Inc., Cary, NC) and Stata, version 9 (StataCorp LP, College Station, TX).

Ethics Statement

The study was approved by the Ministry of Health of the Government of Zambia, the Research Ethics Committee of the University of Zambia and the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health.

Results

Comparison of HIV-infected children receiving care at the outreach clinics before and after transfer

A total of 111 HIV-infected children were referred to one of the outreach clinics before September 1, 2011, and caretakers of 77 children completed the outreach questionnaire. The median age of the children at study entry was 3.4 years (IQR: 1.7, 7.7) and 47% were male. Almost all caretakers (99%) reported that it was easier to get to the outreach clinic compared to Macha Hospital because they did not have to travel as far (100%), had lower travel costs (56%), and transportation to the outreach clinic was easier (67%). After transfer to the outreach clinic, travel time was significantly shorter (p<0.0001). The proportion of children travelling more than five hours to get to the clinic decreased from 29% to 4% (figure 1).

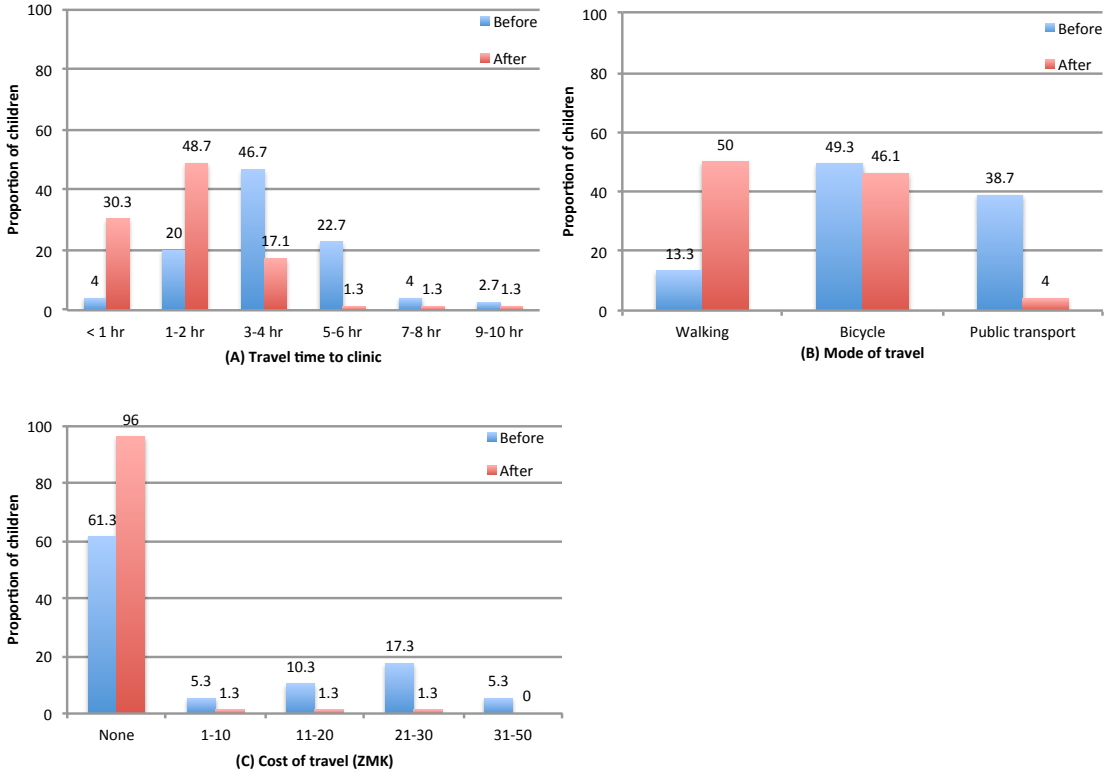


Figure 1. Travel time (a), mode (B), and cost (C) before an after transfer to outreach clinics
(ZMK= Zambian Kwacha, rate 1 ZMK=0.2 US$)

The proportion of children requiring public transport, as opposed to walking or using a bicycle, decreased from 39% to 4% (p<0.0001). Consequently, caretakers reported lower transportation costs and had fewer difficulties in finding transportation after transferring to the outreach clinic (91% vs. 21%; p<0.0001). The proportion of caretakers reporting no costs associated with travel increased from 61% to 96% (p<0.0001).

The majority of caretakers (83%) perceived the overall quality of care at the outreach clinics to be the same as the hospital. When asked about specific components of care, however, many perceived aspects of care at the outreach clinics to be different. Most caretakers perceived the waiting time to be shorter (85%), but some reported the counseling services (34%) and physical examination (26%) in the outreach clinics to be of lower quality than at the hospital clinic.

Table 1. Characteristics of HIV-infected children receiving ART at the hospital or outreach clinics.

	Hospital Clinic (n=41)	**Outreach Clinics (n=68)**	**p-value**
At entry	n (%)	n (%)	
Male	19 (46.3)	37 (54.4)	0.41
Median age in years (IQR)	4.9 (2.2, 9.4)	2.9 (1.6, 7.5)	0.07
<1	3 (7.3)	7 (10.3)	
1-1.9	7 (17.1)	16 (23.5)	
2-4.9	11 (26.8)	19 (27.9)	
5+	20 (48.8)	26 (38.2)	0.70
Status of parents			
Both alive	22 (53.7)	51 (75.0)	
One parent alive	15 (36.6)	10 (14.7)	
Both parents died	4 (9.8)	7 (10.3)	0.30
Other household member receiving ART	21 (52.5)	43 (64.2)	0.23
SES quartile			
1st (lowest)	28 (68.3)	41 (60.3)	
2nd	10 (24.4)	26 (38.2)	
3rd	2 (4.9)	1 (1.5)	
4th (highest)	1 (2.4)	0 (0.0)	0.21
Highest level of education of primary caregivers[a]			
None	0 (0.0)	2 (3.1)	
Primary	19 (55.9)	43 (67.2)	
Secondary	14 (41.2)	19 (29.7)	
College / technical training	1 (2.9)	0 (0.0)	0.20
At ART initiation			
Median age in years (IQR)	5.9 (2.4, 10.4)	2.9 (1.7, 7.3)	0.03
< 1	3 (7.3)	6 (8.8)	
1-1.9	4 (9.8)	17 (25.0)	
2-4.9	11 (26.8)	20 (29.4)	
5+	23 (56.1)	25 (36.8)	0.15
Median WAZ (IQR)	-1.7 (-2.5, -0.7)	-2.3 (-3.6, -1.3)	0.07
Underweight	12 (41.4)	34 (58.6)	0.13
Median CD4% (IQR)	14.4 (11.0, 19.5)	14.2 (10.5, 18.9)	0.91
Severe immunosuppression	23 (62.2)	36 (65.5)	0.75
ARV regimen			
AZT/3TC/EFV	10 (25.0)	15 (22.4)	
AZT/3TC/NVP	3 (7.5)	15 (22.4)	
D4T/3TC/EFV	16 (40.0)	24 (35.8)	
D4T/3TC/NVP	16 (40.0)	24 (35.8)	
Other	3 (7.5)	2 (3.0)	0.31

[a] among respondents who were primary caregivers, n=98

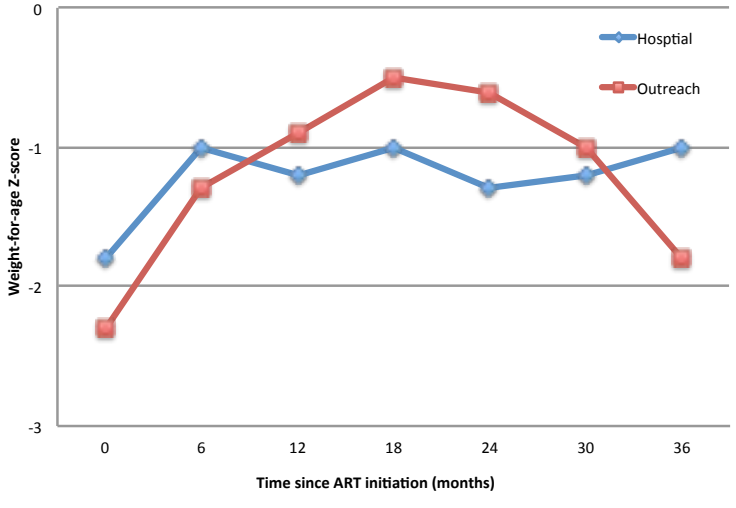
Comparison of HIV-infected children receiving ART at the hospital and outreach clinics

Characteristics of the population at study entry and ART initiation

Forty-one children in the hospital group and 68 children in the outreach group received ART during the study period, of whom 34 and 48, respectively, initiated ART during the study period. Children in the outreach group were similar to the hospital group at study entry, except they were more likely to be younger (median age: 2.9 vs. 4.9 years; p=0.07) and have both parents alive (75% vs. 54%; p=0.03) (Table 1). At ART initiation, children in the outreach group were more likely to be younger (median age: 2.9 vs. 5.9 years; p=0.03) and to have a lower WAZ (median WAZ: -2.3 vs. -1.7; p=0.07) (Table 1).

Clinical, immunological and virological responses to treatment

Children in the outreach and hospital groups were followed for a median of 32.3 (IQR: 22.3, 38.8) and 33.5 (IQR: 23.1, 42.6) months in the study while receiving ART (p=0.50). Among children in the outreach group, the median time between study enrolment and transfer to the outreach clinic was 9.1 months (IQR: 3.9, 14.4), and children received care at the outreach clinic for a median of 23.8 months (IQR: 12.2, 32.4) during the study. Thirty-nine children started ART at the hospital clinic and two children started ART at the outreach clinic.

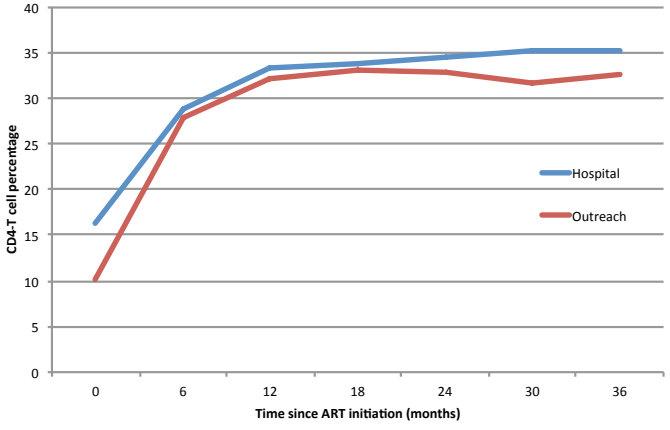


Hospital N	67	58	48	36	26	16	10
Mean WAZ	-1.8	-1.0	-1.2	-1.0	-1.3	-1.2	-1.0
Outreach N	1	7	24	29	27	18	12
Mean WAZ	-2.3	-1.3	-0.9	-0.5	-0.6	-1.0	-1.8

Figure 2. Mean weight-for-age z-score since ART initiation for HIV-infected children at the hospital or outreach clinics (Note: outreach treated as time-varying covariate)

Children in both groups responded well to ART. Mean WAZ increased from -1.8 at ART initiation to -1.0 after three years among children receiving care at the hospital clinic and from -2.3 to -1.8 among children receiving care at the outreach clinic (Figure 2). Using longitudinal models, children in both groups experienced similar trajectories in WAZ over time, with WAZ increasing in the first six months and then plateauing. In the first six months, mean WAZ, adjusted for age at ART initiation, increased 0.11 (SE: 0.02) per month among children receiving care at the hospital and 0.08 (SE: 0.08) per month among children receiving care at the outreach clinics (p=0.70) (Table 2). After six months of ART, WAZ did not significantly change (mean increase per month: hospital clinic group: -0.003; outreach clinic: -0.003; p=0.97).

Mean CD4+ T-cell percentage increased from 16.3% at ART initiation to 35.2% after three years among children receiving care at the hospital clinic and from 10.1% to 32.6% among children receiving care at the outreach clinic (Figure 3). Longitudinal models showed that both groups experienced similar trajectories in CD4+ T-cell percentage over time, with CD4+ increasing in the first six months and then remaining relatively stable. In the first six months, mean CD4+ T-cell percentage, adjusted for age and WAZ at ART initiation, increased 1.97% (SE: 0.13) per month among children receiving care at the hospital, and 1.42% (SE: 0.43) per month among children receiving care at the outreach clinics. After six months of ART, CD4+ T-cell percentage did not significantly change (mean increase per month: hospital clinic: 0.07%; outreach clinic: 0.05%; p=0.66) (Table 2).



Hospital N	79	68	56	39	31	23	17
Mean CD4 %	16.3	28.8	33.2	33.8	34.6	35.3	35.2
Outreach N	2	8	26	37	33	23	13
Mean CD4 %	10.1	27.9	32.2	33.0	32.8	31.7	32.6

Figure 3. Mean CD4+ T-cell percentage since ART initiation for HIV-infected children at hospital or outreach clinics (Note: Outreach treated as time-varying covariate)

Viral suppression was assessed up to three years after ART initiation. The proportion of children with undetectable viral load was lower among children receiving care at the outreach clinics at each time point, although samples sizes were small and few differences were statistically significant (Table 3). After 24 and 36 months of treatment, the proportion of children with undetectable viral load was 90% and 82% among those receiving care at the hospital and 77% (p=0.18) and 77% (p=0.77) among those receiving care at the outreach clinics. Fifty-five children in the outreach group and 29 in the hospital group had at least two viral load measurements after a minimum of six months on ART to assess virologic failure. Ten children in the outreach group (18.2%) and one child (3.5%; p=0.06) in the hospital group experienced virologic failure. The ten failures in the outreach group occurred before (n=3) or after (n=8) transfer to the outreach clinic.

Table 2. Changes in CD4+ T-cell percentages and weight-for-age z-scores among children receiving ART at hospital or outreach clinics

	Crude			Adjusted		
	Hospital Clinic	**Outreach Clinics**	**p-value**	**Hospital Clinic**	**Outreach Clinics**	**p-value**
CD4+ T-cell percentage (CD4%)						[a]
CD4+ T-cell percentage at ART initiation (SE)	17.9 (1.00)	23.7 (3.64)	0.12	25.7 (3.62)	28.8 (4.59)	0.31
Increase in CD4+ T-cell percentage per month in first 6 months of ART (SE)	1.8 (0.12)	1.1 (0.48)	0.15	2.0 (0.13)	1.4 (0.43)	0.20
Increase in CD4+ T-cell percentage per month after 6 months of ART (SE)	0.07 (0.03)	0.009 (0.05)	0.16	0.07 (0.03)	0.05 (0.05)	0.66
Weight-for-age z-score (WAZ)						[b]
WAZ at ART initiation (SE)	-1.97 (0.18)	-1.60 (0.54)	0.50	-1.70 (0.51)	-1.27 (0.74)	0.44
Increase in WAZ per month in first 6 months of ART (SE)	0.11 (0.02)	0.09 (0.07)	0.78	0.11 (0.02)	0.08 (0.08)	0.70
Increase in WAZ per month after 6 months of ART (SE)	-0.003 (0.007)	-0.002 (0.009)	0.90	-0.003 (0.007)	-0.003 (0.009)	0.97

[a] adjusted for age and WAZ at ART initiation
[b] adjusted for age at ART initiation

Table 3. Plasma HIV vrial loads over time among children receiving ART at hospital or outreach clinics

Month on ART	**Hospital Clinic**		**Outreach Clinics[a]**		**p-value**
	N	**% undetectable VL**	**N**	**% undetectable VL**	
3	44	90.9	3	100.0	0.59
6	61	90.2	6	100.0	0.42
9	34	94.1	8	50.0	0.001
12	52	94.2	24	87.5	0.31
15	12	100.0	12	91.7	0.31
18	28	100.0	29	82.8	0.02
21	10	100.0	15	93.3	0.40
24	30	90.0	26	76.9	0.18
27	1	100.0	2	50.0	0.39
30	12	91.7	16	81.3	0.44
33	2	100.0	1	0.0	0.08
36	11	81.8	13	76.9	0.77

[a] Outreach treated as a time-varying covariate

Adherence

The proportion of children with full adherence (>95%) at each study visit tended to be lower for those receiving care at the outreach clinics compared to the hospital clinic, although no significant differences were observed (Additional file 1). When considering all visits after ART initiation (combining visits at the hospital and outreach clinics for children in the outreach group), children receiving care at the outreach clinic had significantly poorer adherence. The median percentage of visits with full adherence was significantly lower in the outreach compared to the hospital group (69.2% vs. 79.3%; p=0.01) and the proportion of children with full adherence at all study visits was lower in the outreach group compared to the hospital (24.6% vs. 32.5%; p=0.35). When adherence among children in the outreach group was further investigated, no significant difference in adherence was found before and after transfer to the outreach clinics. The median percentage of visits with full adherence was 75% (IQR: 50, 100) before transfer and 75% (IQR: 43, 100) after transfer (p=0.81). The proportion of children with full adherence at all visits before transfer was 39% and 34% after transfer (p=0.59).

Additional file 1. Adherence over time among children receiving ART at the hospital or outreach clinics

	Hospital Clinic		**Outreach Clinics**		**p-value**
	N	**>95%**	**N**	**>95%**	
% Adherence; Month on ART[a]					
3	68	69.1	6	50.0	0.34
6	71	63.4	6	83.3	0.33
9	60	75.0	17	64.7	0.40
12	55	81.8	24	70.8	0.27
15	46	78.3	25	64.0	0.19
18	40	75.0	28	75.0	1.00
21	34	85.3	33	69.7	0.13
24	32	81.3	28	75.0	0.56
27	31	71.0	26	73.1	0.86
30	25	80.0	16	62.5	0.22
33	22	86.4	24	66.7	0.12
36	18	66.7	16	75.0	0.28
Median % of visits with good adherence	40	79.3	65	69.2	0.01
% children with good adherence at all visits	40	32.5	65	24.6	0.38

[a] Outreach treated as a time-varying covariate

Retention in care

At the end of the study, after a median of 34 months on treatment, 75% of children in the outreach group and 95% of children in the hospital group were active in the program. Among children followed at the hospital clinic, none died or were lost to follow-up and two children (4.9%) were transferred to other clinics. Among children followed at the outreach clinics, one died from drowning (1.5%) and none were lost to follow-up. The primary reason for departure from the program in the outreach group was transfer: four children (5.9%) were transferred to other clinics and 12 children (17.6%) were transferred to Chilala Clinic when it became an independent ART clinic.

Discussion

Decentralization from higher to lower level health facilities and task-shifting from higher to lower level care providers are essential if access to HIV care is to increase in resource-limited countries in the face of rising patient numbers and declining donor funding [7]. Many challenges remain, however, to sustaining decentralized ART programs and site-specific strategies will be required to achieve optimal provision of care [36]. In this evaluation of mobile and hospital-based HIV care for children in rural southern Zambia, transfer to the outreach clinic resulted in a significant decrease in travel time and costs. Children receiving care at the outreach clinics had similar clinical and immunological response to treatment compared to children receiving care at the hospital clinic, but were more likely to experience treatment failure.

Distance to the clinic and transportation were barriers to retention in care in rural southern Zambia and elsewhere [25, 30], with levels of attrition increasing with travel distance [37]. One multisite analysis in western, eastern and southern Africa found that the risk of attrition doubled if travel time to clinic exceeded 2 hours [25]. Even for children receiving care at the hospital clinic, distance to the clinic was previously shown to be associated with an increased risk of virologic failure [31]. As HIV care is lifelong, making services more accessible and providing them in a familiar environment increases health-related quality of life and satisfaction with clinical services [38], and increases the likelihood of retention in care.

Several decentralized HIV treatment programs reported similar or better outcomes in HIV-infected adults [7-9, 21, 22] compared with those treated at hospital-based HIV clinics. A recent study in five countries in sub-Saharan Africa also reported significantly lower rates of loss to follow-up (adjusted rate ratio: 0.55) and mortality (adjusted rate ratio: 0.66) among children cared for at primary health centers compared to secondary or tertiary health centers [17]. However, other studies reported higher mortality among HIV-infected adults and children cared for at health centers compared to hospital clinics [6], and higher percentages of adults with detectable viral load among those followed in primary health clinics [16], consistent with our findings in children. As adherence is closely associated with viral suppression [26], this may have been due to the lower adherence observed in this group.

In discussions with the outreach team, important differences emerged between the hospital and outreach sites in the cadre of clinical staff and infrastructure. The HIV clinic at the hospital employs on average three trained psychosocial counselors to provide adherence and other counseling to adults and children. Only one counselor was part of the outreach team. Because of the limited healthcare personnel at the outreach clinics, the counselor was involved in other tasks, such as patient screening and vital signs measurement. The counselors felt that they were not able to spend sufficient time with each child and caregiver, and could not provide the same quality of counseling services as at the hospital clinic. In addition, a dedicated space for counseling was not available and the lack of privacy compromised the ability to provide optimal care.

As the goal is to achieve the same quality of ART services at the outreach clinics [29], additional measures are needed to ensure that children receive the same standard of care. Increased efforts on the part of government and donors may be needed to expand support for formal basic health worker training, recruitment and retention [39] so that staff at rural health clinics can provide high quality HIV care and treatment. The more recent involvement of community volunteers, including members of surrounding communities who are HIV-infected, has helped outreach clinics conduct patient tracing and record heights, weights, and vital signs using digital equipment. Other innovative

programs have used peer educators or adherence support workers to improve adherence counseling with good results [40, 41]. Mobile health technologies, including the use of personal digital assistant devices, may also be useful in the expansion of ART access in resource-poor settings with limited human resources [42]. The use of a mobile computer-based decision support program could enable lay-workers to coordinate care in the community and promote effective task-shifting.

There were several limitations to this study. First, this was an observational study in which children were transferred to the outreach clinics at various times after starting treatment at the request of the caregiver. Only children who responded well to treatment were eligible for transfer and therefore the outreach group represented a select group of children. As a valid comparison group, children of caretakers who named Macha Hospital as their rural health center were selected. Differences in characteristics were adjusted for in the analysis but unmeasured differences between the groups may have remained. Second, the sample size was small, particularly at longer follow-up times and for virologic outcomes. Children with viral load measurements were slightly underrepresented in the hospital group. Lastly, this study was conducted at one hospital and outreach clinics in three rural districts in Zambia. The generalizability of the results to other settings may be limited.

Conclusions

This is one of the few studies of HIV-infected children conducted in rural sub-Saharan Africa comparing treatment outcomes between different service delivery approaches. HIV care and treatment can be delivered to HIV-infected children at rural health centers through mobile ART teams, removing potential barriers to uptake and retention. With the limited infrastructure and healthcare personnel, however, there is the potential for the quality of services, particularly counseling, to be compromised, potentially jeopardizing treatment outcomes. Further support is needed to ensure children receive optimal care in rural settings with limited resources

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Chapter 10

Feasibility and Challenges in Providing Antiretroviral Treatment to Children in Sub-Saharan Africa

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Abstract

The scale-up of pediatric antiretroviral therapy (ART) in sub-Saharan Africa over the past decade involved unprecedented political and donor commitment. These pediatric ART programs have demonstrated they can provide ART to human immunodeficiency virus (HIV)-infected children and that these children achieve treatment outcomes comparable to children in high-resource settings. Several obstacles, however, have hindered program implementation and impacted treatment outcomes.

Challenges particularly affecting children include shortages of properly trained healthcare providers, lack of laboratory capacity for infant diagnosis and pediatric treatment monitoring, poor adherence, disclosure of HIV infection status and attrition. Innovative solutions to these challenges have been developed and programs are demonstrating they can successfully expand services to increase ART coverage in affected communities.

As programs optimize the care and treatment of children, and more efficiently provide HIV services within the health care system, new challenges arise, including integration of child and family health services, use of electronic health records and the potential need for rationing antiretroviral drugs. Further evaluation of innovative solutions to these challenges and barriers to care, as well as continued commitment on the part of governments and donors, will be required if all HIV-infected children are to receive proper care.

Introduction

Over the past decade great strides have been made in providing care and treatment to human immunodeficiency virus (HIV)-infected children in resource-limited settings, particularly in sub-Saharan Africa, home to 90% of the estimated 2.5 million HIV-infected children [1]. Globally, the estimated number of children receiving antiretroviral therapy (ART) increased from 75,000 in 2005 to over 356,000 in 2009 [2]. This success was possible as a result of the establishment of funding mechanisms to provide ART and the infrastructure to effectively deliver these drugs, including support from the World Bank Multi-country AIDS Programme (MAP), the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), and President Bush's Emergency Plan for AIDS Relief (PEPFAR). Other factors important for the rapid scale-up of ART programs included provision of generic antiretroviral drugs at reduced cost and collaborations between multiple stakeholders and organizations enabling government officials and health care providers to overcome some of the obstacles to providing complex treatment to children in resource-limited settings.

While these represent great successes, the estimated ART coverage for eligible HIV-infected children globally is only 28% and lags behind the estimated 37% coverage for adults [2]. Pediatric ART coverage in sub-Saharan Africa is lower, at 26%, although substantial regional variation exists, with an estimated coverage of only 12% in Western and Central Africa compared to 32% in Eastern and Southern Africa [2]. While many challenges to providing ART to HIV-infected individuals in such settings exist, provision of ART to children presents unique obstacles. Many challenges have been identified and examples of locally-adapted strategies to overcome these challenges have been documented. New obstacles will be encountered as ART programs expand and as eligibility for ART widens. For example, new technologies have been adopted in resource-limited settings to improve infant diagnosis and treatment guidelines have been revised such that all HIV-infected children are eligible for ART in the first two years of life [3]. These changes will increase demand for pediatric HIV care and treatment services, placing more strain on overburdened health care systems.

In light of these current and future challenges, we review the feasibility and effectiveness of pediatric ART in sub-Saharan Africa, highlighting some of the successful practices and developments in service delivery and care.

Pediatric Antiretroviral Therapy in Sub-Saharan Africa

Feasibility of Pediatric Antiretroviral Therapy in Sub-Saharan Africa

When ART programs were implemented in sub-Saharan Africa, not all national guidelines encouraged the widespread scale-up of ART for children as some believed pediatric ART was too complicated and difficult for clinicians to manage [4]. Administration of ART to children is complicated by the need for pediatric drug formulations, changing dosages with age and body weight, more technologically advanced diagnostic tools for infants (i.e. nucleic acid detection), the use of CD4+ T-cell percentages to initiate and monitor ART responses, and healthcare personnel trained in use of pediatric ART. At the time ART programs were established, most of these issues had not been resolved and pediatric drug formulations were not available. Despite these difficulties, many regions chose to include children in ART programs, overcoming dosage obstacles by using split-tablet adult formulations for children [4, 5].

Resources for pediatric ART have increased since ART programs were first implemented. Pediatric drug formulations, even in fixed-dose combinations, are now available, many programs can measure CD4+ T-cell percentages to inform ART initiation and monitoring decisions, and many programs have access to HIV DNA testing for early infant diagnosis. With these improvements, the estimated number of children receiving ART in sub-Saharan Africa increased from 85,000 in 2006 [6] to 296,000 in 2009 [2]. Programs continue to scale-up and expand, and with new evidence supporting the benefits of early initiation of ART for infants and children [7], treatment guidelines have been revised so that more children are eligible for treatment (Table 1) [3, 8- 10].

Table 1. World Health Organization Pediatric Treatment Guidelines

	Age-specific guidelines			
WHO 2003 [c]	**<18 months and CD4 available**[a,b]	**<18 months and CD4 not available**[a,b]	**≥18 months and CD4 available**[b]	**≥18 months and CD4 not available**[b]
	WHO stage 2 or 3 and CD4<20%	Treatment not recommended	WHO stage 3 Or WHO stage 2 (CD4<15%) Or WHO stage 1 and CD4<15%	WHO stage 3 Or WHO stage 2 (TLC<1500 cells/mm^3)
WHO 2006 [d]	**≤11 months**	**12 – 35 months**	**36 – 59 months**	**≥5 years**
	WHO stage 3 or 4 Or WHO stage 1 or 2 and CD4<25% or <1500 cells/mm^3 or TLC<4000 cells/mm^3	WHO stage 3 or 4 Or WHO stage 1 or 2 and CD4<20% or <750 cells/mm^3 or TLC<3000 cells/mm^3	WHO stage 3 or 4 Or WHO stage 1 or 2 and CD4<15% or <350 cells/mm^3 or TLC<2500 cells/mm^3	WHO stage 3 or 4 Or WHO stage 1 or 2 and CD4<15% or <200 cells/mm^3 or TLC<2000 cells/mm^3
WHO 2008 [e]	**Infants <12 months**	**12 – 35 months**	**36 – 59 months**	**≥5 years**
	All	WHO stage 3 or 4 Or WHO stage 1 or 2 and CD4<20% or <750 cells/mm^3	WHO stage 3 or 4 Or WHO stage 1 or 2 and CD4<20% or <350 cells/mm^3	WHO stage 3 or 4 Or WHO stage 1 or 2 and CD4<15% or <200 cells/mm^3
WHO 2010 [f]	**Infants <12 months**	**12 – 23 months**	**24 – 59 months**	**≥5 years**
	All	All	CD4≤25% or ≤750 cells/mm^3	CD4<350 cells/mm^3

WHO: World Health Organization; TLC: total lymphocyte count
[a]where virologic testing is not available; [b]WHO used a 3 stage classification in 2003; a 4 stage classification was adopted in 2005
[c]Ref.[8]; [d]Ref.[10]; [e]Ref.[9]; [f]Ref.[3]

Effectiveness of Pediatric Antiretroviral Therapy in Sub-Saharan Africa

While the benefits of pediatric ART in high-resource settings are well-documented, concerns were raised that children in sub-Saharan Africa may not experience similar benefits due to differences in environmental, clinical, immunological and virological characteristics. Children in sub- Saharan Africa are more likely to be orphans and to have poorer access to healthcare, including HIV diagnostic, care

and treatment services, affecting the stage at which children access treatment and their ability to adhere to treatment regimens [11]. In addition, untreated children in sub-Saharan Africa have higher levels of comorbid conditions, including malaria, tuberculosis, helminths and undernutrition, more rapid disease progression and higher HIV viral load. All of these factors contribute to the poorer survival of untreated HIV-infected children in sub-Saharan Africa compared to children in high resource settings, and could affect treatment responses [11].

Despite these differences, studies of the effectiveness of ART among HIV-infected children in sub-Saharan Africa indicate that treatment outcomes similar to those observed in Europe and North-America can be achieved in the first few years after the initiation of ART [11-14]. Viral suppression was achieved by most children in sub-Saharan Africa within the first 6 months after ART initiation and was maintained throughout follow-up for up to 2-3 years [12]. A recent meta-analysis of treatment outcomes among 14 studies in Africa, Asia and the Caribbean found that the estimated proportion of children with virologic suppression 12 months after initiating ART was 70% (95% CI: 67-73) [14]. CD4+ T-cell percentages increased by an estimated 13.7 percentage points (95% CI: 11.8, 15.7) 12 months after starting ART in this study [14], and have been found to be relatively stable thereafter [12]. Weight-for-age z-scores also increased after initiation of ART, such that the proportion of children who were underweight was reduced by 30-80%; however, similar increases in height-for-age z-scores were not observed [13]. Mortality was generally low and was highest in the first 6 months after ART initiation [12, 13]. A pooled analysis of 16 sites across sub-Saharan Africa found that cumulative probabilities of death for HIV-infected children receiving ART at 6, 12, and 24 months were 4.8% (95% CI: 4.0, 5.8), 6.0% (95% CI: 5.0, 7.1), and 6.9% (95% CI: 5.9, 8.1), respectively [15].

Several important differences exist regarding the characteristics of HIV-infected children enrolled in care and treatment in sub-Saharan Africa compared to children in high resource settings [12, 13]. The majority of children in sub-Saharan Africa were older, with most studies reporting a median age greater than 5 years, and initiated treatment at a late stage of disease, with most children exhibiting World Health Organization (WHO) stage 3 or 4 disease and a CD4+ T-cell percentage of less than 15%. In addition, levels of undernutrition were high, with most studies reporting a median weight-for-age z-score less than -2 [12, 13].

These studies indicate that most children enrolled in ART programs in sub-Saharan Africa are a subset of children who survived the first few years of life and had signs of disease progression before accessing HIV care. However, children who accessed treatment services and initiated ART experienced reductions in morbidity and mortality comparable to those observed in high-resource settings. These ART program experiences in countries throughout sub-Saharan Africa demonstrate that ART can be effectively administered to children in these settings. However, approximately one third of children receiving ART developed virologic failure one year after starting therapy [14], highlighting the need for low cost, effective second line antiretroviral drug regimens. Finally, more data are needed on long-term virologic responses to ART in HIV-infected children in sub-Saharan Africa.

Challenges and Solutions to the Provision of Antiretroviral Therapy to Children in Sub-Saharan Africa

Providing ART and scaling up ART programs is challenging in resource limited settings, and many obstacles are faced that can hinder program implementation and impact treatment outcomes. Challenges that particularly affect children include shortages of properly trained health care providers, lack of laboratory capacity for infant diagnosis and treatment monitoring, adherence, disclosure of HIV infection status and attrition. With experience gained in implementing pediatric ART programs in sub-Saharan Africa over the past decade, innovative solutions to address and overcome these obstacles have been developed. While these challenges impact most programs, the solutions are context-specific. Programs need to determine the most appropriate solution for their setting.

Programmatic Challenges and Solutions

Human Resources

One of the primary factors limiting the scale-up of ART programs is the shortage of trained health workers. The WHO estimates that over 4 million health workers are needed to address the global shortage, with much of the need in sub-Saharan Africa [16]. While this region is home to approximately 67% of the global burden of HIV-infected persons, only 3% of the world's health workers and less than 1% of world health expenditure are in sub-Saharan Africa [16]. Shortages in this region are compounded by uneven distribution of the workforce, with the majority of the population living in rural areas while most health workers are located in urban areas [17]. The shortage is particularly acute for pediatric HIV care and treatment as healthcare workers require specific knowledge of the diagnosis and management of HIV infection in children. Many do not feel comfortable or adequately trained to manage HIV exposed or infected infants and children.

To address the shortage of health workers while maintaining quality health care, the WHO recommended implementing task shifting, whereby specific tasks are assigned to health workers with less training and lower level qualifications [16]. Allowing non-physicians to provide care and treatment services to HIV-infected children has enabled ART services to be decentralized, such that they can be provided at health centres in addition to hospitals, and takes advantage of existing healthcare infrastructure and resources.

Many programs have implemented task shifting to facilitate the scale-up of ART services. A recent review of task shifting identified 24 programs that implemented some form of task shifting in Malawi, Zambia, Rwanda, South Africa, Nigeria, Democratic Republic of Congo, Uganda, Kenya, Lesotho, and Mozambique [18]. Many programs engaged new cadres of workers, including lay or peer health workers trained to perform non-medical tasks, such as patient counselling, adherence monitoring and contact tracing. Non-physician medical officers, including clinical officers in Zambia, técnicos de medicina in Mozambique, and medical assistants in Malawi, received additional medical training and assumed tasks traditionally assigned to physicians. Task shifting was found to reduce program costs and increase program efficiency [18]. By allowing senior staff to concentrate on more complicated patients and issues, clinic waiting times were reduced and more patients accessed ART services [18].

An important concern with task shifting is the potential for decreased quality of care. The evidence indicates, however, that this has not happened and that quality can, in fact, improve as errors are minimized and patients are more thoroughly evaluated in a less burdened system [18, 19]. In addition, good clinical outcomes were observed in these programs [18, 19]. However, several reports emphasized the burden of training, supervising and mentoring lower level health care workers, and highlighted the importance of investing in these activities to ensure high quality care [18, 19].

While task shifting has allowed for the scale-up of pediatric ART programs, it is not a long-term solution in the face of a shortage of health workers at all levels. Investments must be made to strengthen health systems and train health workers, including physicians, nurses, pharmacists and laboratory technicians, to provide care and treatment to HIV-infected children. This can be accomplished by increasing class sizes and fast-tracking training, but for many countries this will also involve the development of new programs and institutions. In addition, opportunities for continuing medical education need to be provided so that health care workers maintain their knowledge and skills, and are informed of new developments in pediatric diagnosis, drug formulations, and management. Several methods of providing ongoing training are available. E-learning can provide a relatively inexpensive and effective way of learning on-site [20]. Training can be provided through distance learning courses, OpenCourseWare, or telemedicine, where consultative advice and training are provided through online conferences with experts around the world, as demonstrated in the HIV online provider education program (HOPE) [21]. Another method is to provide off-site training to selected health workers who are instructed to return and provide on-site training to their peers, as demonstrated in the PALSA-PLUS project in South Africa for primary health care nurses [22]. In this way, service interruptions from off-site training of staff are minimized.
Addressing shortages in human resources will be critical for pediatric ART programs to expand, particularly into rural areas. This will require innovation and ongoing investment, commitment and collaboration between governments, academic institutions and national and international organizations.

Laboratory Diagnosis and Monitoring

Clinical laboratories play a critical role in the care and treatment of HIV-infected children, including the timely diagnosis of HIV infection, disease staging, diagnosis of opportunistic infections and monitoring treatment responses. With the rapid scale-up of HIV treatment programs, many countries in sub-Saharan Africa are poorly equipped to deal with the increasing demand for laboratory services and are limited by both physical and human resources [23, 24]. Donor funds have become available to upgrade laboratory facilities at many regional and district hospitals and to train staff in the performance of laboratory tests and equipment maintenance. This has been accomplished in some areas through partnerships with institutions in high-resource countries, such as the partnership between the Institutes of Human Virology in Nigeria and the University of Maryland [25]. Nevertheless, laboratory capacity remains limited in many regions, particularly in rural areas, where a consistent supply of clean water, electricity, trained staff and reagents remains challenging.

The laboratory capacity for diagnosing HIV infection and monitoring treatment responses remains particularly problematic for children. Early infant diagnosis is complicated by the fact that it cannot

be done with the antibody-based assays used to diagnose older children and adults, but requires polymerase chain reaction (PCR)-based technology currently available in centralized laboratories. Early identification of HIV-infected children is critical for their timely entry into comprehensive care, as early treatment initiation reduced infant mortality by 76% and HIV disease progression by 75% [7]. Consequently, the WHO now recommends ART for all children under the age of 2 years regardless of clinical or immunologic status [3].

As most facilities do not have the capacity for early infant diagnosis, samples must be sent to centralized laboratories. The use of dried blood spots (DBS) has made this process simpler, as samples can be obtained directly from a heel or finger prick and stored and transported at room temperature, reducing costs and resources [26]. However, the turnaround time for specimens transported to central laboratories can be lengthy. Transportation of specimens can be problematic, particularly in rural areas, where road systems may be inadequate and impassable during rainy seasons. In addition, fewer children require diagnostic assays than adults and the small number of samples may lead to fewer batches sent to central facilities and longer turnaround times for results, delaying diagnosis and treatment.

As the importance of early infant diagnosis has been recognized, much work has been done to develop simpler assays requiring less sophisticated technologies that could be performed in peripheral facilities. The ultrasensitive HIV-1 p24 antigen enzyme-linked immunosorbent assay, for example, has high sensitivity and specificity, can be used with DBS, and does not require specialized equipment or training [27, 28]. Point-of-care assays are also being developed that are inexpensive and can be performed in most facilities by trained healthcare workers. Several new approaches are based on nanotechnology and microfluidics, and include biobarcode amplification-based assays, microfluidics-based viral detection and quantification, miniaturized PCR chips, miniaturized immunoassays, point-of-care HIV-1 amplification systems and point-of-care DNA extraction systems [29, 30].

Monitoring treatment responses, both with immunologic and virologic measures, is important to detect treatment failure, which occurs more frequently in children than adults receiving ART [31]. The capacity to measure immunologic responses with CD4+ T cell percentage has become more accessible, such that many smaller facilities outside regional and district hospitals have the capacity to perform these assays. However, monitoring virologic responses requires more sophisticated and expensive technology and is still restricted to centralized laboratories. Consequently, monitoring treatment failure is either done by clinical and immunologic criteria alone or blood samples are sent to centralized laboratories for HIV viral load testing. Neither of these options is ideal. Good immunologic responses without complete viral suppression are common among children, leading to poor sensitivity and specificity of the immunologic and clinical criteria and delays in the detection of virologic treatment failure [32]. As for PCR-based diagnostic assays, the turnaround time for specimens transported to central laboratories can be lengthy, resulting in delayed detection of treatment failure.

The need for simple, low-cost assays to monitor HIV viral load in low-resource countries has been recognized and several new assays have been developed with significantly lower costs, including the Cavidi ExaVir RT assay [30, 33, 34] and the Ultrasensitive p24 assay [30]. Both assays are ELISA-based and measure viral activity (reverse transcriptase or p24 antigen), which are correlated with HIV viral load. While these assays reduce cost, the ExaVir RT and Ultrasensitive p24 assays are time consuming and labor intensive [30]. As for diagnostic assays, point-of-care assays are being

developed that could be used to monitor HIV viral load [30]. While the lack of laboratory facilities, personnel and assays has not prevented the scale-up of ART programs, they are critical to their success in providing quality care and treatment to HIV-infected children. With new treatment guidelines for children [3], early infant diagnosis will become even more important and challenging. Countries will need to continue to enhance laboratory capacity until simpler, low-cost, point-of-care assays are available.

Patient Care Challenges and Solutions

Adherence

High levels of adherence to antiretroviral drugs are necessary to prevent emergence of drug resistance [35]. Adherence among adults receiving ART is challenging due to social, logistical and personal factors but adherence among children is further complicated by their partial or complete dependence on caregivers, and is therefore determined by the motivation and ability of the caregiver to administer the medication, the willingness of the child to take the medication and the social dynamics within the family. Adherence is also difficult to measure, particularly in children in resource limited settings, as direct measures of adherence using plasma drug levels and more objective, indirect measurements, such as electronic devices (e.g. Medication Event Monitoring System (MEMS) [36]), cannot be used due to expense and the lack of laboratory capacity.

In addition, pediatric fixed dose combinations have only recently become widely available; therefore, children take many drugs in different formats (pills and syrups), making it more difficult to provide a combined measure of adherence. Researchers must often use more subjective, indirect measures of adherence, such as self, caregiver or health worker reports, pill counts or measurements of syrup volume, pharmacy records and visit compliance.

In two recent reviews of pediatric ART adherence in low income countries, adherence was generally high and compared well with studies of adherence in high income countries [12, 35]. Estimates of adherence, defined in various studies as taking >85%, >95% or 100% of doses, ranged from 49% to 100%, with only four studies reporting rates less than 75% [35]. The difficulties in measuring pediatric adherence, however, have led to heterogeneity in measures and definitions of adherence used in different studies, making comparisons difficult. In general, studies using more objective measures of adherence, such as MEMS, pill counts and visit compliance, found lower levels of adherence than studies using more subjective measures, such as self, caregiver or health worker reports [37-39]. Reported reasons for missing doses included the child forgetting, refusing to take the drugs or vomiting without re-dosing, conflicts between the child and caregiver, insufficient clinic drug stocks, delays in getting new prescriptions due to the cost of transportation, long travel distances and waiting times, incorrect dosing by caregivers, having multiple caregivers involved in administering or supervising drug administration, and issues of disclosure, particularly due to HIV-related stigma [12, 35]. Several social and environmental factors correlated with non-adherence, including living in a rural setting, low levels of parental education, household poverty, non-disclosure to the child or other family or community members, fewer hospital admissions prior to ART, stigma at school, limited caregiver adherence strategies, disorganized families, and no adult caregiver receiving ART [12, 35]. The child's and caregiver's positive attitude toward antiretroviral therapy and

the perceived benefits of the drugs, as well as a supportive relationship with an adult, improved adherence [40].

Given the importance of adherence in achieving good treatment outcomes, many programmes have implemented innovative strategies to improve pediatric adherence beyond the recommended caregiver education through adherence counselling. These strategies attempt to address the complex psychological, social, and family issues affecting pediatric adherence. Several programmes, including the Macha HIV clinic in Zambia [41], TASO in Uganda [42], and Khayelitsha clinic and Ndlovu Medical Centre in South Africa [43, 44], implemented an approach based on directly observed therapy (DOT) developed to increase adherence with tuberculosis treatment. Patients and caregivers are asked to identify a treatment supporter or medicine companion, usually a relative, friend or neighbour, who can assist with adherence by reminding them to administer medications to the child and supporting them in providing care. This form of treatment disclosure and support was reported to be beneficial but has not been formally evaluated.

In addition, training clinic personnel in Macha, Zambia in the quantification of pediatric adherence when children are taking syrups or fractionated tablets, and providing reference charts for appropriate volumes and pill counts, has allowed adherence to be more objectively measured and led to the successful identification of children with sub-optimal adherence who would benefit from counselling [unpublished data].

Other strategies that have been implemented include: 1) child-friendly clinic environments with dedicated clinic days for children, rooms for children furnished with toys, games, videos and colourful decorations, and a playground near the clinic so that children have a place to congregate and participate in group activities led by young peer educators and counsellors [45]; 2) family-centred approaches so that children and their caregivers can be cared for at the clinic and counselled on the same days [45, 46]; 3) group counselling targeted to caregivers, teenagers and children so that each group can share their experiences and receive support from peers [45, 47]; 4) child and teenager fun days where child-friendly social activities are organized through the clinic as a way of strengthening links between providers and patients, providing caregivers and children a forum for establishing social networks [45]; 5) system of reminders, such as pill boxes and alarms [45]; 6) culturally and age appropriate psychosocial support and counselling, using psychotherapy techniques such as sand and art therapy [45]; and 7) training in treatment literacy for caregivers and children to provide the knowledge and skills to better understand, manage and take responsibility for their HIV treatment regimen [45].

Few interventions targeted at improving adherence among children have been formally evaluated. One study in Kenya evaluated the use of medication diaries as a way for children to monitor their own adherence, as diaries improved adherence in adults [48]. However, no beneficial effect of medication diaries was found on self-reported adherence or clinical, immunologic or virologic outcomes. Examples of interventions that have been evaluated in adults include the WelTel study among adults in Kenya investigating the use of mobile phones to improve communication between patients and providers and increase adherence through weekly text messages [49], and modified directly observed therapy (mDOT), involving observed dosing in the mornings during the week and self-dosing in the evenings and on weekends, which was found to significantly increase adherence in Mozambique when supervised by HIV-infected peers [50].

Further research on optimal measures and definitions of pediatric adherence are needed, and standardization would enable comparison across studies and settings. Reporting and evaluation of adherence strategies to improve pediatric adherence in treatment programs would also be helpful so that knowledge can be shared on effective ways to engage and support caregivers and their children and improve adherence to ART.

Disclosure of HIV Status

Disclosure is an issue unique to children as they are not always made aware of their HIV infection status at the time of testing. Information regarding their health and disease status is controlled by the caregiver, and the caregiver must decide when and how to tell the child that they are HIV infected. There are varying levels of disclosure, ranging from no disclosure where the child is not told anything regarding their infection, to partial disclosure where the child is informed that they are sick but not specifically that they have HIV infection, to full disclosure where there is open communication about their disease status [51]. Disclosure is a complex process that may be difficult for caregivers as it raises fears of stigma and discrimination, disclosure of their own HIV status and the possibility that the child might disclose their status to others [51, 52]. However, disclosure can be beneficial for the child as they have higher self-esteem and fewer emotional problems [53]. Disclosure also enables the child to receive support from friends and family and allows the child to participate in their own health care [53, 54], such that they are better able to adhere to their treatment regimens [40, 54-56]. The WHO has recognized this relationship between disclosure and adherence, and recommends that children older than 10 years participate in discussions regarding HIV testing [57].

Research on disclosure in sub-Saharan Africa is increasing and indicates that disclosure is not common, even among older children [53, 58-60]. While caregivers generally report that the optimal age for disclosure is 11 or 12 years [60], only 17-38% of adolescents in Cote d'Ivoire and Zambia were aware of their HIV infection status [53, 58, 59], and many caregivers felt that their children were too young to be told [58]. Significantly more children receiving ART in these studies were aware of their status, as initiating and adhering to treatment often motivate disclosure.

Disclosure is often done by the caregiver [52, 61, 62]; however, healthcare providers play an important role in disclosure by providing support and information regarding HIV infection and treatment, and by maintaining open communication with the caregiver and child. Formal guidelines and recommendations are needed on disclosure to children in sub-Saharan Africa as well as training for healthcare providers and counsellors. For children, disclosure is a long-term process and information must be provided at the appropriate age and stage of development [51]. Healthcare providers and counsellors must be aware of the contextual, social, family and individual issues surrounding disclosure so they can assist caregivers in preparing their children and themselves for disclosure. In this way, children will be better able to cope psychologically and physically with their disease and actively participate in their own care and treatment.

Retention in Care

Attrition in pediatric ART programs is a growing concern as programs scale-up. In addition to ART, children attending HIV clinics receive many health benefits, including preventative and therapeutic treatment for infections and nutritional supplements. Consequently, for children not yet receiving ART, failure to remain in care increases the risk of disease progression and opportunities for

treatment may be missed. For children receiving ART, intermittent use of ART increases the risk of developing drug resistance, limiting future treatment options.

A pooled analysis of 16 sites across sub-Saharan Africa found that attrition was relatively high, with estimated cumulative probabilities of loss to follow-up at 6, 12, and 24 months of 2.6% (95% CI: 2.0, 3.4), 5.0% (CI: 4.1, 6.1), and 10.3% (95% CI: 8.9, 11.9), respectively [15]. More recent studies have found even higher rates of attrition, with losses of 11.5%, 17.0% and 24.7% at 18 months in Southern, East and West Africa, respectively [63]. The reasons for loss to follow-up among children are not completely understood. Among adults, a recent meta-analysis of patients lost to follow-up found that only 63% could be successfully traced [64]. Among those who were traced, 40% had died, with substantial heterogeneity across studies (range: 12% to 87%), and mortality was most likely to occur within the first 30 days after discontinuing care [65, 66]. Common reasons for not returning to the clinic included transfer to another clinic, financial barriers (i.e. for transportation or child care), and improved or deteriorating health [64-66].
Few studies investigated reasons for attrition among children; however, a substantial proportion of children lost to follow-up likely died or transferred to another clinic. One study conducted in rural and urban Zambia examined factors associated with loss to follow-up and found significantly higher rates of attrition among children who were ineligible for ART at presentation [67]. Distance to the clinic was associated with attrition for both eligible and ineligible children, with higher rates of attrition for children living farther away from the clinic. In the same study population, distance to the clinic was negatively associated with viral suppression [68]. Both direct and indirect costs of transportation have been identified as barriers to adherence in adult and pediatric populations, particularly in rural areas where distances travelled may be substantial [58, 69-73].

As for adherence, retention in a treatment program is more complicated for children than adults, as children must often rely on a caregiver to take them to the clinic and pharmacy. Consequently, strategies to improve retention must consider the needs and motivation of both the child and the caregiver. Several models of care have been implemented to improve patient retention. The first is the family-centred approach, which treats the child within the context of the family so that family members can support each other in adhering to treatment regimens and visit schedules [46, 74]. The second is the decentralized model of healthcare delivery, where HIV and ART services are relocated from district hospitals and delivered at peripheral clinics to increase patient access by bringing services closer to their homes, particularly in rural areas. This can be done by providing ART services, including evaluation, treatment initiation and treatment monitoring, at the clinic level, with supervision from a team of physicians or medical officers, as in the Lusikisiki [75], Hlabisa [76], and Mseleni [77] district programs in South Africa, nurse-based programs in Rwanda [78, 79], and the Scott area program in Lesotho [80]. Alternatively, evaluation and treatment initiation can be performed at the hospital level, with subsequent treatment monitoring at the clinic level for children who adequately respond to treatment, as in the Macha, Zambia program [unpublished data]. A third approach is to provide homebased care and ART to HIV-infected individuals with support from clinics, as with field officers in Uganda through TASO [81, 82] and volunteers in a remote area of Tanzania [83], both with favourable results. In these models, retention is encouraged by enabling patients to access services closer to home.
Other interventions that successfully reduced attrition among adults include: 1) the use of cell phones in Cameroon, where patients who received a phone call from a clinician every two weeks in

addition to the standard of care were more motivated to adhere to treatment regimens and remain in care compared with patients receiving only standard care [84]; 2) support and counselling for care and adherence provided by community networks for people living with HIV/AIDS in Malawi [85]; and 3) intensive monitoring of high-risk patients through weekly or bi-weekly rapid contact with nurses in the early phases of ART in Kenya [86].

Future Challenges

As programs overcome the initial challenges of providing pediatric ART and attempt to optimize their services, new challenges will arise. In addition, the needs of the population may change as new guidelines, technologies and treatments are introduced. Three challenges that many pediatric programs may face in the near future include integrating child and family health services, introducing electronic medical records systems and inadequate funding resulting in the rationing of care and treatment.

Integration of Child and Family Health Services

Provision of ART to children in sub-Saharan Africa needs to be tailored to local circumstances and attention given to the distinct role of each level of the healthcare system. Integration of pediatric HIV care within primary health care has been limited, with vertical programs independently managing prevention of mother-to-child transmission (PMTCT), immunizations, integrated management of childhood illnesses (IMCI), tuberculosis diagnosis and treatment, infant diagnosis of HIV infection and ART services. The functional and frequently structural separation of these services hampers the continuum of care and results in high attrition rates between the component services.
The integration of HIV/AIDS services into the primary health care system in Mozambique provides an example of how this can be accomplished to improve HIV care and strengthen the primary health care system [87]. ART services were located in existing health facilities in 23 districts, primary health care workers were retrained, laboratory services and referral mechanisms were improved, HIV and antenatal services were integrated, and district level management was strengthened. Three years after implementation, loss to follow-up from the time of HIV testing in antenatal and tuberculosis clinics to entry into ART services declined from 70% to less than 10% in many sites and the time from HIV testing to treatment was shortened.

Scale-up of pediatric ART requires that testing and care be provided in peripheral health centres and integrated into the primary health-care system, reducing the burden on hospital clinics and improving access for patients living in rural areas. As a simple example, recording data related to
HIV infection (including exposure and testing) on the child's under-5 card, as recently introduced in some countries (e.g. Zimbabwe and Zambia) [88], is a step toward partial integration of HIV and routine child health care. Further integration in Zambia was attempted through a National Management of Pediatric HIV Clinical Mentorship program to decentralize pediatric HIV services and increase the coverage of HIV infected children receiving treatment from 8% nationally. After two years it was concluded that on-site, pediatric clinical mentorship models need to be comprehensive and focus not only on the provider's knowledge but also on clinic delivery systems. Without

including system improvements, the scale-up of comprehensive pediatric HIV services will remain stagnant [89].

Undernutrition is common among HIV-infected children accessing care in sub-Saharan Africa and has been associated with disease progression and death in untreated children and with increased mortality in children receiving treatment [12]. Pediatric ART programs often do not have access to consistent food supplements. Integrating nutritional assessment with HIV care is essential and can be done by performing routine anthropometric assessments, including use of weight-for-age charts. Proper referral for nutritional counselling can assist in identifying causes other than lack of food and result in increased energy intake [90]. Sufficient attention should be given to training healthcare workers providing care to HIV-infected children in nutritional counselling. Partnering with organisations with the resources to provide nutritional supplementation can assist in improving the nutritional status of HIV-infected children.

Bringing Pediatric ART Programs into the Electronic Era

To provide high quality and continuity of care to HIV-infected children, and efficiently manage pediatric ART programs, clinicians and administrators need to be equipped with appropriate information [91]. ART programs provide care to hundreds of children over thousands of clinic visits, and methods of summarizing and aggregating that information in a meaningful way is needed. Electronic medical records (EMR), linking clinical, pharmacy and laboratory data, fulfil that need and can be useful for all data users: clinicians, administrators, donors and researchers. Clinicians need to access a child's complete medical history in a structured and easily accessible format to provide better care, make more informed medical decisions and avoid medical mistakes. Administrators need to view data aggregated at the clinic level to facilitate program planning and anticipate future clinic and pharmacy needs by providing data on trends in clinic enrolment and prescription practices. Programs need to monitor retention by generating lists of children who missed appointments and should be traced, and to generate reports to satisfy donor requirements. Finally, researchers need to access de-identified individual or aggregated data to conduct observational research studies. Several EMR systems have been implemented in sub-Saharan Africa, including the AMPATH medical record system in Kenya [91-93], OpenMRS in South Africa, Kenya, Rwanda, Lesotho, Zimbabwe, Mozambique, Uganda, and Tanzania [94-96], the Patient Management Information System (PMIS) in Malawi [97], the HIV-EMR (based on OpenMRS) in Rwanda [98, 99], and SmartCare in Zambia, Ethiopia and South Africa [100]. Experience with OpenMRS in Uganda showed that implementation of the EMR increased the amount of time that clinicians spent in direct patient care and decreased patient waiting times [96].

While some medical record systems still use paper-based forms, which are then entered into the EMR system, others, such as SmartCare and PMIS, are working towards fully electronic systems with clinicians entering data directly into computers. There also is interest in integrating HIV clinic records into the larger health record, with links between programs and only one unique ID per child, such that any clinician caring for the child would have access to the medical record. SmartCare is working toward implementing a comprehensive EMR system using electronic cards provided to each patient that contain the electronic health record updated at each point of service [100]. Programs also are exploring the use of cellular technology to assist patient follow-up, dissemination of laboratory test results and adherence to medications [49, 100, 101].

While EMR systems are essential to the scale-up of pediatric ART programs, computerization of ART facilities will be challenging. In resource-constrained settings, computers will need to be updated and maintained, and will require a constant supply of electricity. Web-based systems will require a reliable internet connection, and, as with all record systems, the value of the EMR will depend on the quality of the data entered. An evaluation of EMR systems in the ART-LINC database examined the proportion of missing data on key patient characteristics and found heterogeneity across sites, with up to 9.9% missing age at ART initiation, 37.2% missing clinical stage and 53.0% missing baseline CD4+ T cell count [102]. The proportion of missing data was found to correlate with the number of hours spent by data clerks and the findings emphasized the need for well-trained and competent staff to manage the database and perform data entry. The value of the EMR system also will depend on the ability of users to access the data. Many systems are designed to readily produce reports for donors, but would be most useful if clinicians, administrators and researchers could access the data.

Inadequate Funding Resulting in Rationing of Pediatric Antiretroviral Drugs

Rationing antiretroviral treatment in low and middle-income countries is increasing as funding from international donors has stalled. Several countries in sub-Saharan Africa have reported turning patients away due to deficits in both domestic and international funding [103]. If the current funding situation persists, rationing will negatively impact the successes pediatric ART programs have achieved in the last ten years by limiting the number of new children initiating ART and the quality of care for children receiving ART.

Establishing guidelines as to when ART should be initiated is a way of allocating scarce resources. However, treatment guidelines for infants and children have become progressively wider. With renewed efforts to diagnose HIV infection in infants and young children, the number of children in need of ART will continue to grow. In addition, while expansion and increased effectiveness of programs to prevent mother-to-child transmission will reduce the number of children infected with HIV, the number of HIV-infected children with prior exposure to antiretroviral drugs will increase, necessitating the use of more expensive second-line drugs [104]. Consequently, if current funding levels persist, it will only become more difficult to provide ART to children, undermining efforts to promote HIV testing for children and confidence in the healthcare system.

Conclusions

The roll out of ART in sub-Saharan Africa over the past decade has involved unprecedented political and donor commitment. Despite the many barriers to implementation in such settings, programs have demonstrated they can provide ART to HIV-infected children and these children have similar treatment outcomes as children in high-resource settings. Pediatric ART programs have developed innovative solutions and are demonstrating they can successfully expand services to increase ART coverage in affected communities (Panel **1**). As programs optimize care and treatment, and more efficiently provide HIV services at health centres, new challenges will arise. Further evaluation of ART programs will be necessary to identify these new challenges and barriers to care, and continued commitment on the part of governments and donors will be required if all HIV-infected children are to receive proper care.

Panel 1. Challenges and Solutions to the Provision of Antiretroviral Therapy to Children in Sub-Saharan Africa

Challenges and solutions

Programmatic challenges and solutions

1. Human resources for pediatric ART
   Solutions:
   - Implement task shifting
   - Increase enrolment in graduating classes for all categories of health workers
   - Create new programs to train health workers
   - Provide continual training of health workers through innovative training methodologies, such as e-learning, telemedicine and 'train the trainers' approaches
2. Laboratory capacity for infant diagnosis and monitoring of pediatric ART
   Solutions
   - Expand laboratory capacity for HIV diagnosis and monitoring
     - Partner with institutions in high-resource settings
   - Develop simple, low-cost point-of-care assays for infant diagnosis and viral load monitoring

Patient care challenges and solutions

1. Pediatric adherence to ART
   Solutions:
   - Implement use of treatment supporters
   - Identify reliable low-technology, low-cost methods of assessing adherence
   - Train clinic personnel in ways to measure pediatric adherence
   - Implement family-centred approaches
   - Provide group and psychosocial counselling for caregivers and children
   - Provide adherence reminders, such as pill boxes, alarms, and text messages
   - Provide training in treatment literacy
2. Disclosure of HIV infection status
   Solutions:
   - Develop formal guidelines on disclosure
   - Train healthcare providers and counsellors to discuss disclosure with caregivers and children
3. Retention in care and treatment
   Solutions:
   - Implement models of ART delivery that promote retention
     - Family-centred approaches
     - Decentralized models of care
     - Home-based models of care

Future challenges

1. Integrating child and family health
2. Bringing pediatric ART into the electronic era
3. Inadequate funding to sustain and expand scale-up of pediatric care and treatment

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Part Five:
Summary and General Discussion

Chapter 11

A: Summary

Introduction

This thesis presents data of a collaboration between different partners: Macha Research Trusts (previously called Malaria / Medical Institute at Macha) and Macha Mission Hospital in Macha, Zambia; AIDS relief Zambia and the Zambian Ministry of Health; Erasmus MC, University Medical Center Rotterdam, the Netherlands; and the Bloomberg School of Public Health, John's Hopkins University, Baltimore, USA.

Macha Hospital is one of the about 1,769 health facilities providing HIV and AIDS services in Zambia [1]. The hospital is unique due to the long history of community work, and the collaboration with the adjacent research institute, all situated in a rural village in Zambia. The data of the paediatric HIV cohort group receiving care at this rural Zambian hospital provides the basis for this thesis. Although most studies of HIV-infected children in sub-Saharan Africa are conducted in urban areas [2], where resources and infrastructure are greatest, the studies presented in this thesis were conducted in a rural community within the context of the observational cohort study of primarily perinatal infected children (PART study) that has been ongoing since 2007. While conducting research in a rural setting is challenging because of limited resources, these studies provide insight into the long-term consequences of HIV infection and treatment and the unique barriers and challenges associated with providing care and treatment in this setting.

In this final chapter, we will summarize the presented studies, highlight some of the achieved successes and remaining challenges regarding paediatric HIV-care in resource-limited settings, and conclude with future perspectives.

Summary of main findings

Part one - Introduction

Following the general introduction **[chapter 1],** we present a systematic review of published data on the effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan African, which places our data in a broader perspective. This literature review, presented in **chapter 2**, demonstrated that *short-term results* of sub-Saharan treatment programs are promising. In view of the rate at which ART program expansion has taken place in the sub-Saharan region, achieving similar program outcomes in sub-Saharan Africa to those seen in developed countries is a significant accomplishment. However the older age and greater disease severity at the time of treatment initiation in sub-Saharan African HIV-infected children hindered direct comparisons with children in Western countries.

Late identification of clinically ill HIV -infected children supports the need for earlier diagnosis and treatment. Increased access to easy-to-use technologies for diagnosing HIV infection in children, strengthening of counseling and testing programs, as well as PMTCT programs, and revised criteria so that children become eligible for ART at less severe stages of immune suppression are urgently needed.

More than half of the children reported were undernourished at treatment initiation. This calls for integrated models of care addressing malnutrition and including both therapeutic and supplementary feeding.

Suboptimum antiretroviral regimens were usually available for use, with only 63% of the studies reporting the use of protease inhibitors. The need for increased access to paediatric drug formulations, including fixed-dose combinations, and increase in the availability of effective second-line drugs for children was described.

Reported results were from treatment programs implemented in urban centers. Continued advocacy is needed to increase access to care for HIV-infected children, particularly in rural populations, with the need to evaluate and monitor these programs as well.

The review provides evidence that the sub-Saharan treatment programs are effective in delivering viral suppression, patient retention and survival, confirming universal treatment access as an attainable key policy priority. Initial ART outcomes showed great promise for the future, but there is no room for complacency. Many obstacles still remain on the road to universal access.

Part two - Barriers to care in rural Zambia

One of the major barriers to care in rural sub-Saharan Africa is access to health facilities. In this rural setting, lack of transportation (54%), insufficient financial resources (60%) and bad roads (32%) were commonly cited obstacles to accessing the clinic, particularly during the rainy season **[chapter 3].** The majority of caregivers either walked or used a bicycle and over 25% travelled more than 5 hours to get to the clinic.

Disclosure of HIV infection status to children was infrequent. Few children, even among the older age groups, were reported to be aware of their HIV-infection status, with only 3% of all children reportedly aware of their HIV infection status, and 17% of those 10 years or older. Children receiving ART were more likely to be aware of their status (33% vs. 6%). The majority of caregivers felt their child was too young to know their infection status while others were afraid to tell their children or did not know how. This information was reported by the caregiver rather than the child and may be

an underestimate of the children's true knowledge of their status, but it at least shows the limited involvement of the caregiver in the disclosure process at that time.
Children in rural Zambia had a substantial rise in CD4+ T cell counts in the first year of ART and later analyses of the same cohort showed that two years after initiating ART these gains were sustained.
Weight gain among the HIV-infected children receiving ART in rural Zambia did not achieve the levels reported elsewhere in sub-Saharan Africa. Developing strategies to improve access to care and nutrition will be necessary to ensure optimal, long-term treatment outcomes for HIV-infected children residing in rural sub-Saharan Africa.

To determine if the limited access in rural areas, due to the unique challenges faced by providers and patients, affects the care and treatment response, we compared characteristics at HIV clinic enrollment, time to ART initiation, and treatment response between children accessing HIV-care at urban versus rural clinics **[chapter 4].** The majority of both urban and rural children presented with advanced disease and - immunosuppression. Unexpectedly, and contrary to similar comparisons of urban, peri-urban and rural adults, children in the urban areas presented at a more advanced clinical and immunological stage of disease.
Long distances to travel in the rural areas influenced the timing of visits as well as program attrition, with loss-to-follow-up being high among children living further away from the clinics, especially among children ineligible for treatment. Both urban and rural children responded well to treatment, consistent with other studies [chapter 2]. The level of immunologic and clinical response was influenced by their differing baseline characteristics. Factors associated with higher risk of mortality included attending a rural clinic, younger age, lower WAZ, WHO stage 3 or 4, and low (<5%) CD4 T-cell percentage at ART initiation. However, in a multivariate analysis, attending a rural clinic was no longer significantly associated with mortality, while the other mentioned baseline characteristics still were. Mortality was consistently higher in rural clinics, partly due to the younger age and higher levels of malnutrition. Loss to follow-up was higher in the urban clinic and was associated with the same risk factors as mortality. It is possible that the increased mortality in the rural areas partly can be explained to more successful contact tracing and ascertainment of outcome.

Part three - Treatment responses in rural Zambia

Additional to the results of the earlier cross-sectional analysis in the PART study cohort [chapter 3], the study assessing treatment outcomes during the first two years of ART **[chapter 5]** confirmed that ART can effectively be delivered in a rural setting and demonstrates that children experienced sustainable immunologic and virologic improvements after initiating ART. Early gains in CD4+ T-cell percentages were maintained throughout follow-up.
The study also demonstrates improvements in enrollment and treatment of children at younger ages, who had better clinical and immunological profiles and less severe stages of disease progression.
In summary, children initiated ART with a mean CD4 T-cell percentage of 16.3% and experienced an initial increase of 1.8 percentage points per month in the first 6 months of ART. Subsequently, CD4 T-cell percentages increased at a slower rate of 0.23 percentage points per month. The majority (82%) of children achieved a CD4 T-cell percentage in the normal range (>25%) within the first year of ART.
Adherence to ART was high, with approximately 75% of children reporting >95% adherence to medication. Increased travel time negatively impacted the likelihood of achieving viral suppression

among children receiving ART, although the majority of children (87%) achieved persistent viral suppression within the first two years of treatment. The observed detrimental effect of long travel times on virologic suppression may have implications for ART delivery in this setting. As treatment programs expand further into rural areas, clinic catchment areas will expand. Unless decentralized models of care are implemented, children may continue to have to travel great distances for their care and treatment, which may impact both their ability to remain in care and respond to treatment.

As found in the previous analysis [chapter 4], higher levels of undernutrition were observed in this rural population as compared to other studies. In the study evaluating the growth patterns **[chapter 6]** of young HIV-infected children in rural Zambia with good immunologic recovery on ART, both weight and height-for-age significantly improved after initiation of ART. Differing patterns of improvement of WAZ and HAZ were associated with undernutrition and age at ART initiation, respectively. Underweight children experienced a greater increase in WAZ in the first 6 months of ART, and children older than 5 years at initiation experienced significantly smaller increases in HAZ per month compared to children younger than 2 years of age. However, a large proportion of children were underweight (60%) and stunted (72%) at ART initiation and remained underweight (45%) and stunted (46%) after two years of treatment, higher than observed among HIV-negative children in the same region [3]. Consequently, successful treatment with ART was not able to fully reverse the effects of HIV and undernutrition on growth. Partnerships between HIV treatment and nutrition programs should be explored so that children receive an integrated care and treatment approach that includes nutritional support. Further evaluation of the impact of food supplementation on growth after ART initiation is needed.

Part four - Service delivery

The majority of children enrolling in HIV care and treatment programs are already eligible for ART at the time of enrollment [chapter 4], as was 60% of children in the study looking at mortality rates and clinical predictors of mortality during the period prior to ART initiation **[chapter 7]**. While mortality rates differ between programs depending on the characteristics of the population and the rigor of ascertainment of deaths, estimates indicate that a significant proportion of children entering care are dying before they initiate ART. In this study, the cumulative mortality prior to ART initiation was 13.3% and was comparable to the cumulative mortality of 14.4% among children initiating ART in this paediatric cohort [chapter 5]. In addition, the mortality rate in the first three months after study enrollment among children eligible for ART was comparable to the mortality rate in the first three months after ART initiation (unpublished data). In this study factors associated with mortality included younger age, anaemia and lower WAZ score at study enrolment and were similar among children eligible and ineligible for ART at study enrolment.

This mortality rate remains unacceptably high in the context of ART, and mortality from paediatric HIV contributes significantly to overall child mortality, especially in high-burden countries. The benefits for children on ART should be the same whether in a resource-poor or -rich setting, yet the death rate among the former is eight times that of the latter [4]. This underscores the need to increase efforts to identify HIV-infected children at an earlier age and stage of disease so they can enroll in HIV care and treatment programs prior to becoming eligible for ART. In this way, they and their family can be prepared to initiate life-long therapy and receive the full benefits of treatment.

Antiretroviral treatment (ART) options for young children co-infected with HIV and tuberculosis are limited in resource-constrained settings due to limited data on the use of efavirenz (EFV). Consequently, there is a need for alternative treatment strategies for young children with tuberculosis and data to support their use. Given the limited antiretroviral treatment options in these settings for children receiving rifampicin and the need to initiate ART as soon as possible to avoid excess morbidity and mortality, an EFV dosing schedule extrapolated from available pharmacokinetic data was developed for the clinical care of young children co-infected with tuberculosis. This dosing schedule was implemented as the standard of care at Macha Hospital in the Southern Province, Zambia and was independent of the observational cohort study. Treatment outcomes in children younger than 3 years of age or weighing less than 10 kg, receiving either EFV-based ART plus anti-tuberculous treatment or nevirapine-based (NVP) ART were compared **[chapter 8].** Despite poorer health at ART initiation, children younger than 3 years of age who were treated for tuberculosis and received an EFV-based ART regimen showed significant improvements in clinical, immunological and virologic outcomes, comparable to young children receiving a NVP-based regimen.
Given the increasing number of young HIV-infected children starting ART in sub-Saharan Africa, the high burden of tuberculosis, the limited treatment options in this region, and the limited virologic efficacy of NVP, use of EFV in young children can be considered. This is the first study to demonstrate that EFV can be used effectively in young HIV-infected children with tuberculosis. Additional studies will be required to validate and optimize an EFV dosing strategy for young children co-infected with TB.

In chapter 2, we showed that travel distance and time are barriers to care for HIV-infected children in resource-poor settings. Decentralization is posed as being one of the keys to scaling-up access to antiretroviral treatment, and in **chapter 9** we evaluated such a program comparing treatment outcomes for children receiving care in mobile and hospital-based HIV clinics in rural Zambia. We found that, despite similar clinical and immunologic outcomes, children in the outreach group were less likely to achieve virologic suppression, which potentially could be due to lower adherence. Continuous emphasis on the quality of services provided and the importance of adherence is critical for the success of decentralized care.

The disparity between paediatric and adult access to treatment is large as provision of ART to children presents unique obstacles. Multiple challenges have been identified, and examples of locally-adapted strategies to overcome these have been documented. **Chapter 10** reviews the feasibility and effectiveness of pediatric ART in sub-Saharan Africa, highlighting some of the successful practices and developments in service delivery and care. Bottlenecks that particularly affect children and limit paediatric treatment are discussed in this chapter, including shortages of properly trained health care providers, lack of laboratory capacity for infant diagnosis and treatment monitoring, adherence, disclosure of HIV infection status, and retention in care.
Addressing shortages in human resources is critical for paediatric ART programs to expand, particularly in rural areas. To increase access to ART, WHO promotes task shifting where non-specialist cadres take on responsibilities in the ART management [5]. Many programs have implemented some form of task shifting, giving a reduction in program costs and increasing program efficiency. However, supervision and mentoring are of importance to ensure high quality of care (see also chapter 9).

Clinical laboratories play a critical role in the care and treatment of HIV-infected children. The need to expand laboratory capacity and to develop simple, low-cost point-of-care assays for infant diagnosis and viral load monitoring has been recognized and mentioned in the above.

Consistent adherence to dosing guidelines by health care providers and patients is essential to reduce the likelihood of treatment failure from under dosing or drug toxicity from overdosing. In children, correct dosing is more challenging as it depends on close monitoring of growth through accurate weight and height. Many programs have implemented innovative strategies to improve pediatric adherence beyond the recommended caregiver education through adherence counseling. These include the implementation of treatment supporters; training clinic personnel in ways to measure pediatric adherence; identify reliable low-technology, low-cost methods of assessing adherence; implement family-centered approaches; provide group and psychosocial counseling for caregivers and children; provide adherence reminders, and provide training in treatment literacy.

The relationship between disclosure and adherence is recognized and WHO recommends that children older than 10 years participate in discussions regarding HIV testing [6]. However, research indicates that disclosure is not common in sub-Saharan Africa. Formal guidelines and recommendations on disclosure to children, as well as training of health care providers and counselors to guide in this process are needed to increase the level of disclosure among children in sub-Saharan Africa.

As for adherence, retention in care is more complicated for children than for adults. Consequently, strategies to improve retention must consider the needs and motivation of both the child and the caregiver. A family-centered approach, decentralized model of care, and a home-based model of care are some of the models that have been implemented to improve patient retention.

Some of the future challenges for paediatric programs that were identified include integration of child and family health services, introducing electronic medical records systems, and inadequate funding.

B: General Discussion and Future Perspectives

The objective of this thesis is to address the knowledge gap that currently exists in rural sub-Saharan Africa on barriers to care, disease progression and treatment outcomes of HIV-infected children. As many HIV-infected children reside in rural areas in sub-Saharan Africa, these studies provide insight into the unique barriers and challenges associated with providing care and treatment in this setting, and potential solutions, so the long-term health and well-being of these children and youth can be attained.

Children in resource-limited settings respond to treatment as well as those in resource-rich settings. The vast difference in outcomes is the result of both biomedical and program factors and include having advanced disease upon diagnosis, other co-infections, malnutrition, and delays in starting ART. However, the challenges to curb the HIV epidemic among children in rural sub-Saharan Africa are still enormous. Ways to further improve access to care and ensure optimal and long-term treatment outcomes for HIV infected children residing in rural sub-Saharan Africa in the (near) future, can be divided into:

1. Improving early identification of HIV-exposed children and access to early infant diagnosis *(PMTCT, linkage, point-of-care diagnostics)*;
2. Supporting the expansion of ART programs into rural areas to increase access to treatment services and reduce inequities (*targets, integration, decentralization, task-shifting)*;
3. Integrating HIV care and treatment approach that includes nutritional support;
4. Optimizing care to attain sustained immunological and virologic improvements *(disclosure, adherence, access to optimal treatment regimens and monitoring)*;
5. Improving retention in care

(1) Improving early identification of HIV-exposed children and access to early infant diagnosis *(PMTCT, linkage, point-of-care diagnostics).*

It is essential to recognize the critical link between paediatric prevention and paediatric treatment. With more than 90% of children infected with HIV through mother-to-child transmission (MTCT) [7], scaling up interventions to prevent MTCT is to be central to the goal of eliminating new paediatric infections. Significant progress has been made in the global scale-up of prevention of mother-to-child transmission of HIV (PMTCT), in high burden and resource-limited settings. For the first time, the elimination of MTCT (eMTCT) is now considered a realistic public health goal [8]. The world has now embarked on a historic effort to end new HIV infections among children and reduce the number of women living with HIV who die from pregnancy-related causes. Stakeholders have joined together to develop the *Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive* [9], which is an effort to reduce new HIV infections in children by 90% over the next years through improved access to PMTCT, maternal treatment and infant testing.

Pregnant women are eligible for ART for their own health if CD4 count < 350 or WHO stage 3 or 4. WHO has recommended 2 different PMTCT options, from which countries can choose.

Option A is for HIV-infected pregnant women who are not in need of ART for their own health. ARV prophylaxis option A consists of antepartum twice-daily zidovudine (AZT), plus single dose nevirapine (sd-NVP) at the onset of labour plus twice-daily AZT + lamivudine (3TC) during labour and delivery and continued for 7 days postpartum. The infant is to receive daily NVP from birth to 1 week after all exposure to breastmilk has ended. For HIV-infected pregnant women who are not eligible for ART for their own health, ARV prophylaxis ***option B*** consists of antepartum daily triple ARV prophylaxis until delivery, or, if breastfeeding, until 1 week after all exposure to breast milk has ended. The infant is to receive daily NPV prophylaxis from birth to 6 weeks of age.
The 2009 WHO guidelines in infant feeding for HIV-infected women is that all mothers who are known to be HIV-infected, either on lifelong ART or not, who exclusively breastfeed their infants should do so for the first 6 months, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life [10]. An AFASS assessment has to be performed before advising women not to breastfeed, to ensure that infant formula feeding is Acceptable, Feasible, Affordable, Sustainable, and Safe.
The abbreviated maternal treatment period in both option A and B, contributes to the high rates of lost-to-follow-up (LTFU) in younger children and consequently higher risks of paediatric mortality, which has been an argument for scaling up a third option of PMTCT, ***option B+*** [11]. Option B+ involves placing all HIV-positive pregnant women on ART for life, regardless of CD4 count, and was initially introduced to sidestep the necessity for CD4 testing of all pregnant women [12]. The option is allike the test and treat mathematical model positioned by Granich and colleagues [13]. Option B+ could result in less HIV maternal-to-child transmission, especially in subsequent pregnancies, as opposed to stop-start methods proposed with option A and B. The total fertility rate in sub-Saharan Africa is high, and soon after the breastfeeding period many women become pregnant again. The majority of women present for antenatal care late in pregnancy, and continuing prophylaxis with HAART would mean that the next pregnancy could be protected from conception. The stopping of ART after cessation of breastfeeding might lead to viral rebound, with the risk of transmission to a sexual partner or fetus being notably raised. In addition, the women on life-long therapy will be healthier with less risk of contracting opportunistic infections, which can prevent the negative paediatric outcomes associated with the decline in health or death of primary caregivers [14]. Universal, lifelong ART for HIV-infected pregnant women will achieve maximum coverage and could potentially lead to elimination of paediatric HIV/AIDS. While studies on clinical, social [15] and economic feasibility of a global scale-up of option B+ for PMTCT have yet to be done, a targeted scale-up of this option in countries with the highest rates of LTFU and mortality could be considered [11].

In order to be able to provide HIV infected pregnant women with the most beneficial regimen to prevent the transmission of HIV to her child, access to CD4 testing is essential. Many HIV treatment programs can now measure CD4+ T-cell levels to inform ART initiation and monitoring decisions, but not all health facilities offering PMTCT services have access to this. Integrated CD4 count service at PMTCT service points, with inexpensive, portable and battery-operated *point-of-care* CD4+ T cell testing technologies can potentially help in avoiding missed opportunities in choosing the optimal PMTCT regimen.

The first step to getting a child on treatment is diagnosis. Weak health and laboratory systems, a limited number of qualified health care workers skilled in paediatric testing, and the stigma around

the possibility of having an HIV-positive child often mean that many infants simply are not being tested for HIV [16]. Many African children have their first health care encounter at a rural primary health care center. Their access to HIV screening depends on timely identification of being at risk for HIV-infection by primary health care workers. To increase EID coverage, different entry points for HIV-exposed infants need to make active referrals (i.e. Maternal & Child Health (MCH) services, HIV care and treatment services, hospital wards, nutrition programs, immunization programs, etc.). This requires collaboration between paediatric and maternal health programs within health care facilities to assure identification of HIV-exposed children, and strengthening counseling on EID during all relevant PMTCT and MCH contacts.

A regular follow-up of HIV-exposed children from the age of 6 weeks on facilitates early HIV testing, timely commencement of cotrimoxazole prophylaxis, infant feeding counseling and, if needed, ART preparedness. There are many benefits from enrolling children long before ART is initiated. In the Macha HIV clinic, HIV-exposed children were tested and referred to the HIV clinic from MCH and paediatric programs and were followed at the clinic until their HIV status could be confirmed. This integration of service enabled the mother to receive her HIV care, and her infant to be attended to at one service point. This more active clinic enrollment procedure has let to children being enrolled in care and initiate ART at a younger age and earlier stages of disease [17].

Despite that this worked well for the Macha clinic, current government guidelines are now requiring PMTCT care provision to be given at primary health care level, and a deviation of this would result in miss-reporting of certain indicators. HIV-infected pregnant women already on full HAART and receiving care at an HIV clinic, do need to bring their child to a different MCH service point for testing and ART prophylaxis if indicated. This does not enable further integration of services and can result in attrition and intermittent service provision for the mother and child. There is a need for the development of indicators for integrated approaches, as well as the integration of existing monitoring systems within different health services, allowing for integration of services with accurate reporting.

HIV disease progresses very rapidly in young children. Without care and treatment, one-third of infants die in the first year and about a half of children by the second year of life [18] (compared to a median survival of 11 years in adults). Early diagnosis of HIV infection enables immediate HIV care and initiation of ART as recommended by WHO, significantly reducing mortality and hospitalization [19], making it imperative to increase access to early infant diagnosis.

Many programs now have access to HIV DNA polymerase chain reaction (DNA PCR) testing for early infant diagnosis, which detects HIV-1 pro-viral DNA integrated in the human genome, and is a more precise option for diagnosing infants and children below 18 months. HIV-exposed infants should be tested at six weeks or as soon as possible thereafter. EID is practically more difficult to deliver as a service than the rapid HIV antibody test. Especially in rural areas, health care facilities do not have the capacity to perform EID themselves, but infant blood samples are sent as dried blood spots to a more centralized laboratory that has the required equipment. The results need to be sent back to sites and returned to caregivers in a timely manner.

In rural Zambia, as elsewhere in sub-Saharan Africa, children accessing care have initially been a subset of HIV-infected children with slower disease progression. At Macha Hospital, infant diagnosis of HIV infection using dried blood spots and PCR was introduced in February 2008, with the aim to reduce the age at which HIV-infected children enter care. For Macha access to EID means sending sample batches to a centralized laboratory in Lusaka, more than 350 kilometers away. We

conducted medical record reviews for children undergoing early infant diagnosis between August 2010 and May 2011 to measure the time from clinic presentation to confirmation of HIV infection in infants evaluated at the HIV clinic in Macha [20]. The median time between specimen collection and arrival at the central laboratory in Lusaka was 13 days (IQR: 8, 18). The median time from arrival at the central laboratory to testing was 5 days (IQR: 3, 5). The median time from arrival at the central laboratory to return of results to the clinic was 23 days (IQR: 9, 35). The median time from arrival of the results at the clinic to return of results to the caregiver was 46 days (IQR: 26, 67), resulting in a total median time from specimen collection to return of results to the caregiver of 84 days (IQR: 82, 92). In summary, the longest delay in diagnosis was in the time required to provide results to caregivers. As the time for transport and testing was variable, and caregivers had to travel long distances to get to the clinic, clinic appointments were often scheduled at three months intervals, and when possible, synchronized visits between children and their caregivers were given. With a more efficient process, caregivers could be provided test results more rapidly, potentially resulting in earlier treatment initiation and better outcomes.
Innovative ways to return results can assist in this – for example SMS messaging and e-mail of results at hub laboratories. The use of mobile phone messages to clients is a promising way to encourage testing, communicate results, and/or give adherence messages. Across rural areas, mobile phone network coverage as well as phone possession by rural women, is still limited and presents big challenges to use this reliably in these settings [21]. Above all, there is a continuous need for point of care diagnostics to truly be able to implement early infant diagnosis, in view of the dramatic survival benefits for infants started on ART as early as possible [19].

(2) Supporting the expansion of ART programs into rural areas to increase access to treatment services and reduce inequities (*targets, integration, decentralization, task-shifting)*;

Children succumb much faster to HIV then adults, yet globally, children infected with HIV have less access to treatment than adults, with barely one in four in need of ART receiving it. The urgency of this situation compels one to look for additional strategies to improve access to paediatric HIV/AIDS care.

Setting time-bound *targets* can help ensure appropriate expectations, planning and accountability. Unfortunately, within the broader treatment roll-out, paediatric targets have been largely neglected in favor of overall ART targets. Furthermore, the 2010 WHO guidelines [22] have expanded the eligibility criteria for children, including recommending ART initiation for all children age two and younger, but many countries have yet to increase their existing paediatric targets to reflect these new recommendations. A step in ending the relative neglect of children infected with HIV, is for countries to set ambitious yet attainable targets for paediatric ART at all levels – national, district, and facility. WHO-UNICEF is proposing that these targets should have an overall goal of at least 80 percent of children in need receiving ART, as children with HIV should at least have equal access to ART as adults [9].

The process of treatment initiation is complex, involving multiple steps and participants. Barriers to

linking a child who is found to be HIV-positive to care and treatment pose challenges, including the effects of stigma and fear, services that do not cater to the entire family's needs, and structural issues facing poor families, such as transportation [16].

Integrating comprehensive prevention and antiretroviral services with maternal, neonatal and child health services can improve the efficiency and effectiveness of all interventions. By packaging services, women are more likely to obtain the services they require and service efficiency will be enhanced [23]. Service integration can especially be beneficial in countries with generalized HIV epidemics since HIV care is a substantial burden for already weak health care systems. A more integrated approach will strengthen the reach and impact of the AIDS response, will leverage HIV-related gains to generate broader health advances and enhance the long-term sustainability of HIV programs [24].

According to a four-year retrospective review of over 200 clinical sites within the Elizabeth Glaser Pediatric AIDS Foundation's (EGPAF) large multi-country HIV care and treatment program in Africa [25] the following were associated with favorable paediatric enrolment and a high proportion of children under two years of age on ART: nutritional support, early infant diagnosis, linkages with associations of people living with HIV, and on-site PMTCT services. These findings showing the link between certain services and favorable program outcomes for children suggest areas of clinical activities that might be expanded or strengthened so leading to improved paediatric HIV service utilization among similar resource-limited country populations.

Additionally, involving affected communities, innovation and commitment will be required to alleviate the stigma that would deter women living with HIV and vulnerable women from attending antenatal care and child services. Community support programs that complement clinical services and mentor mothers, support disclosure, promote the involvement of men and boys and reduce stigma and discrimination are all critical to promote access to essential services and retain families in care [24].

Recent improvements in early infant diagnosis and revisions to the WHO paediatric treatment guidelines to broaden the eligibility criteria for initiating ART [21] mean that more HIV-infected children will be identified, started on ART and survive into adolescence and adulthood. We should aim to provide the kind of integrated medical care that is essential in order to fully serve paediatric patients with HIV infection over the long term. While there is consensus about the need for more integrated systems health service delivery, a range of factors at policy and service-delivery levels have been identified as challenges to deliver integrated care. At the policy level, these include vertical programming, lack of policy guidance on integrated care, under-funding of some program areas, program territorialism, and weak referral systems. At the service level, factors can include high patient load, staff shortages and insufficient training and skills in certain program areas, resistance to change, and inadequate monitoring systems related to integration. Actions are needed at both policy and service-delivery levels to develop an integrated approach, and national policies to deliver HIV treatment within a primary care context can be used to promote more integrated approaches [26].

HIV-infected children in rural southern Zambia have long travel to access care [chapter 3] and long travel times influenced program attrition [chapter 4], and had a detrimental effect on virologic suppression [chapter 5]. *Decentralization of care and task shifting*, where HIV and ART services are relocated from hospitals and delivered at peripheral clinics, can be an effective strategy to paediatric HIV scale up, follow up and improved retention [27, chapter 9, 10]. By expanding paediatric HIV

training, supporting simplification of paediatric ART regimens, and advocating for task-shifting, decentralization of paediatric HIV care and treatment to primary health facilities can be promoted [28]. For effective decentralization to take place into the rural areas, there should, in addition, be sufficient resources for Primary Health Care Workers (PHCW) to provide the necessary care. In the absence of funds for salary increments, increasing knowledge of motivational strategies, especially for staff from remote centers, is necessary [29]. Stock-taking and distribution of diagnostics and drugs need to be worked out, and a good relationship between communities, traditional leaders and local PHCW is needed, including acceptance of standard HIV-treatment. Traditionally, the rural population have less exposure to media and thus also to HIV/AIDS information. A lot of information, Education and Communication (IEC) material is not adapted to the local culture and is not available in the local language. Consequently there are significant differences in HIV/AIDS knowledge, attitudes and practices between rural and urban population, which need to be understood [30]. A large study comparing paediatric enrollment, ART initiation and early outcomes at primary (PHF) versus secondary/tertiary health facilities (SHF) demonstrated that pediatric care and treatment is feasible in primary health facilities with equally or more effective outcomes than in SHF, highlighting the importance of PHF in the context of decentralization. The low proportion of children < 24 months initiating ART at PHF was concerning, and a multifaceted approach is needed to address this if primary health facilities are to support scale-up of paediatric services [31].

Sub-Saharan Africa has 69% of the world's HIV cases but only 3% of the world's healthcare workforce. The shortage of physicians with paediatric experience has limited expansion of paediatric HIV care and treatment. *Task shifting* (also known as task-sharing) has shown the potential to offer high-quality, cost-effective care to more patients, especially at rural sites, with the added benefits of increasing utilization and reducing loss to follow-up [9]. Steps to be taken towards effective task-shifting and decentralization include; provision of adequate and sustainable training, support and pay for staff in new roles; integration of new members into health care teams; and complying with regulations and policies.

(3) Integrating HIV care and treatment approach that includes nutritional support;

Many studies have documented lower weight and height and impaired growth of HIV-infected children compared to HIV-uninfected children in both high-income [32,33] and low-income settings [34,35,36]. Reasons for HIV-related delays in growth are complex but include alterations in gastrointestinal absorption, chronic or recurrent infections, and endocrine dysfunction [37,38]. Delays are generally more pronounced in children with higher viral loads [39,40] and more severe disease progression [41].

In chapter 2, it was shown that in general there is a high level of malnutrition at treatment initiation among HIV-infected children in sub-Saharan Africa. Further studies among the Zambian cohort demonstrated that the rural children initiated ART at a significant lower WAZ than urban children [chapter 4]. Severe undernutrition was found to be a risk factor for mortality among children eligible for ART as well as for early mortality in those receiving ART [chapter 7]. Treatment with ART resulted in a significant improvement in growth parameters for at least 2-3 years after initiation [chapter2] although a high proportion of children remained underweight and stunted after 2 years of treatment

[chapter 6], and long-term effects on growth and development are unknown, particularly in rural sub-Saharan Africa.
The large proportion of children presenting with malnutrition illustrates the need to develop integrated models of care, combining both therapeutic and supplementary feeding with treatment programs and integrate HIV programs with other care at primary health care level. In this service children would receive integrated disease management, including for malnutrition, with the same counselors and caregivers providing support for ART and nutrition.

Zambia is a relatively politically stable country with plenty of natural resources and a vision of poverty reduction and economic growth; it is therefore an ideal candidate for a country that could make a significant impact on it's malnutrition problem. Nutrition has received political attention and is recognized in overarching development policies and strategies. However, political attention has not moved into concrete action, and each of these strategies, policies, and plans is essentially a wish list noting best practice. The strategies are mainly confined to the health sector, and were created with substantial input from external actors but as for now without the backing of political commitment, budgetary or human resources, or capacity. Nutrition is highlighted as a lower priority area within the health sector, and budgetary allocation to nutrition is thus not prioritized. This hints at a disjuncture between policymaking and reality, and implementation of these grand ideas is severely lacking [42].
Advocacy is needed for mainstreaming food and nutrition as an integral part of comprehensive HIV management and support for those infected and affected by HIV and AIDS. For the effective delivery of nutrition services, including the design, development, and implementation of relevant nutrition programs, projects, and interventions, institutional and human capacity need to be build. Above all, for successful implementation the buy-in from leadership, sector ministries and other stakeholders at national and subnational levels are a necessity.

(4) Optimizing care to attain sustained immunological and virologic improvements *(disclosure, adherence, access to optimal treatment regimens and monitoring)*;

Disclosure is an issue unique to children as they are not always made aware of their HIV status. Whereas chapter 3 showed that disclosure among children in our cohort was not common, a more recent analyses showed a considerable improvement in the child's disclosure status. Full disclosure for children 10 years and older increased from 17% in the 2009 cohort to 48% in the 2013 cohort [Jan 2013, unpublished data]. The availability of paediatric HIV counsellors at the clinic and the increased focus on disclosure is thought to have worked towards this improvement, although we are still only half way to the target of close to 100% of the children within this age-group to know their status.
As HAART becomes increasingly available in low-resource settings, children affected by this disease are living longer, experience a less symptomatic early course of the disease and survive to older ages, with improved quality of life. The increased survival of children on ART in sub-Saharan Africa calls for concerted efforts from researchers and health care providers to develop disclosure guidelines to assist caregivers to disclose to children in a manner that promotes the wellbeing of the child. Intensified information education and communication to de-stigmatize the disease might have

far reaching impact. Caregivers and health providers should have a co-responsibility to decide on the proper time to disclose [43].

Adherence to ART is essential for continued viral suppression but is impacted by individual, family and social factors [44]. Non–HIV disclosure to children has implications for adherence to therapy, resistance and treatment failure. Haberer et al in a study in Zambia [45], noted that older children (9-15 years) with no knowledge of their HIV diagnosis are at risk of treatment failure due to poor adherence. Since adherence means not only following dosing regimens but also being able to refill prescriptions, and since prescriptions are primarily refilled as part of routine follow-up visits, barriers to adherence and retention overlap [46]. Travel distance to clinic sites and associated costs, stigma and fear of disclosure, competing demands for scarce resources, religious and cultural beliefs, and unanticipated obligations and events (e.g. attending a funeral) are key adherence barriers identified through previous research that also bear upon retention [47].

Sustaining ART adherence requires accurate, consistent monitoring, a particular challenge for resource-limited countries. Adherence measurement strategies used in low- and middle-income countries include self- or proxy-report measures, pill counts, pharmacy records, drug levels, clinic adherence and directly observed therapy. The optimal strategy to measure pediatric adherence remains unclear, and adherence estimates vary substantially between sites, but most studies from low- and middle income countries report > 75% paediatric adherence, whereas most studies from high-income countries report < 75% paediatric adherence [44]. The initial levels of adherence in developing countries are encouraging: however, adherence failures may become increasingly common as healthier children gain access and experience the long-term challenges of adherence to ART.

Within the Macha clinic, adherence is measured every visit by pill count and/or liquid measurement. Caregivers are requested to bring their medication bottles each clinic visit. Remaining pills are counted and checked against the number of pills prescribed during the time interval and bottles of liquid medications are weighed. Percent adherence is calculated as the percentage of pills or liquid ingested for each prescribed drug. The process of conducting an accurate pill count and carefully calculating adherence in the presence of child and caregiver may, in itself, reinforce and promote adherence. Adherence assessment using pill count and syrup measurements is more complicated and error prone in children, as weight dependent dosages prevent packaging of standard monthly supplies. Incorporating fractions of tablets and differing doses based on body weight from remaining supplies of prior and current visits make calculations difficult. Calculations are in general made with pen and paper, often using calculator functions on phones. Errors during prescription, dispensing, administration and documentation of treatments are common [48]. Although automated electronic systems might exist for this, with interrupted power supplies in the rural setting it is difficult to fully rely on those.

Research in adherence-promotion strategies within the paediatric HIV population is limited, but clinical experience with paediatric populations is suggesting the benefits of initially determining psychological and psychosocial treatment readiness of child and/or caregiver. Intensive, continuous, coordinated and nurturing case management services are required to produce good outcomes as one-time interventions without ongoing education and support may be insufficient [49].

Improve access to optimal treatment regimens

Once linked to care and treatment, children and families still face challenges. Available HIV drugs are not always formulated for children or easy for caregivers to administer. Their foul taste, frequent dosage, and confusing directions can lead to poor adherence resulting in complications and potential drug resistance.

Whereas HIV treatment used to be very complex, with patients taking handsful of pills 2 or 3 times a day; that is no longer the case, especially for first line treatments and adults. There are single-tablet combination regimens currently available, such that individuals need to take just 1 pill once daily. Patients can continue on this regimen for years if they properly adhere to the treatment. The ART options currently available are also less toxic and easier to tolerate versus older options.

Access to ARV treatment for children has improved steadily since 2005, but at a much slower pace than that for adults. There continues to be significant gaps in the repertoire of ARV drugs needed to deliver comprehensive HIV care to children – especially for infants and for those children who need second or third line therapy. The number of paediatric options available for global programs has increased markedly in recent years with the approval of many new *formulations*, including formulations that meet the unique administration needs of children, such as dispersible fixed-dose combinations (FDCs). Paradoxically, this has not increased the number of *regimen options* that can be given to children, only the number of dosage forms and strengths available to deliver any one particular regimen. By 2012, over 30 pediatric ARV formulations have been WHO pre-qualified, including 8 unique pediatric-strength FDCs and 8 dispersible formulations [9]. WHO strongly endorses the use of FDCs as a general principle to simplify dosing for providers and patients, to improve adherence outcomes, and support decentralizing services. In chapter 5, we were able to confirm that children taking ART regimens including FDC were more likely to be adherent.

The global demand for pediatric antiretrovirals (ARVs) is low as children account for only 7% of all individuals on treatment, and when this low demand is distributed over not only the large number of products available but the numerous dosage forms and strengths as well, demand for any particular product is dramatically reduced. This can result in disruptions in supply chain and threatens the sustainability of the paediatric ART market. Rationalizing pediatric ARV formularies will enhance HIV treatment for children by limiting the risks of stock-outs and ensuring all children are able to benefit from these new formulations [9]. The WHO and UNAIDS “Treatment 2.0” is a global initiative with the objective to achieve universal access for adults and children living with HIV through simplified HIV treatment with optimized drug regimens, point-of-care diagnostics, and decentralized service delivery. A special paediatric working group, lead by WHO, developed an optimized list of paediatric ARV formulations, determining the best options for a limited range of approved and available paediatric ARV formulations that offer the highest quality of care for children of all ages and can be used to deliver all required first and second line ART regimens [50].

Meanwhile, continuous efforts to ensure that adapted treatments reach the children that need them are being made. For example, the Drugs for Neglected Diseases initiative (DNDi) is involved in specific research and development to deliver child-adapted ARV formulations that do not require refrigeration, are easy-to-administer and palatable, with simplified dosing, and which can be given to children co-infected with tuberculosis [51].

Improve access to HIV VL monitoring

As regular HIV-RNA testing is not feasible in many Sub-Saharan African ART programs as in Macha, treatment decisions are frequently solely based on clinical and immunological parameters. However the correlation between these parameters and virological outcomes appears to be marginal. In our study cohort, the children with persistent detectable viral load had no evidence of clinical or immunological failure. As HIV-RNA testing was only available for study purposes, and was performed in batches, these children were not identified as having treatment failure during clinic reviews, and were not yet switched to a second line regimen [chapter 5]. Reports in African HIV-infected children have shown a low sensitivity of clinical and immunological criteria in identifying virologic failure [52,53]. This situation leads to both delayed switching that could encourage further emergence of resistance mutations, and inappropriately premature switching to more expensive second-line agents. Instead, viral load monitoring together with targeted counseling for patients with detectable viral load can promote adherence to treatment, providing an opportunity to delay the onset of HIV resistance [54].

Recent data supports less frequent CD4 monitoring in clinically stable, virally suppressed adult patient and suggests that routine CD4 monitoring for this population may be unnecessary [55]. Reducing the frequency of CD4 cell testing could have benefits for both providers and patients, by saving substantial sums of money (which could be allocated to HIV-RNA testing), and alleviating patient anxiety from fluctuations in serial CD4 test results due to laboratory and physiologic variability. Further research is needed to see if the primacy of viral load monitoring for individuals treated with antiretroviral drugs is also applicable for children, and if a shift from CD4(%) monitoring towards viral load monitoring can be promoted. The development of simpler, cheaper assays and optimizing monitoring strategies based on currently available technologies is thereby critical.

(5) Improving retention in care

Attrition occurs at all points along the care continuum, and in children this stretches from the antenatal period through infancy, childhood, adolescence and, ultimately, through the transition to adult HIV care. With ongoing care and treatment across these stages, the vast majority of HIV-positive children can survive into adulthood. But according to the largest single program multi-country retrospective analysis of children on ART in Kenya, Mozambique, Rwanda and Tanzania [56], barely half of all children having started antiretroviral treatment (ART) at under one year of age were still in care two years later. While at 12 and 24 months, overall 16 and 22% were lost-to-follow-up (LTFU) and 5 and 7% were known to have died at these respective time points, there were significant differences among patient populations. It was suggested these differences result from a combination of factors including national leadership, access to care, HIV prevalence, patient-provider ratios, caseload and decentralization. Factors shown to reduce LTFU, are for example higher staff-to-patient ratios, shorter wait times, and active follow-up.

When looking more into personal and socio-cultural factors associated with the behavior of caregivers who take HIV infected and exposed children for care, thematic content analysis of caregiver's perceptions revealed that their decision about routinely taking their children to HIV care involved multiple levels of factors. The complexity and interconnectedness of these factors underlying retention of children in HIV care by these women caregivers suggests that interventions

to reduce paediatric LTFU need to be holistic and address multiple socio-ecological levels. Patient-centered care that integrates a family-centered approach to HIV paediatric care is therefor recommended [57]. A qualitative research conducted with people with HIV in three African countries [58], found that missed clinic visits may be unintentional or intentional, with complex reasons that change over time. While the initial, practical reasons for non-attendance may pass, people are frequently reluctant to return to the clinic, owing to feeling shame about their absence and in anticipation of negative responses from care providers, ultimately resulting in disengagement from care. The authors recommend that clinicians need to address the reasons patients are reluctant to return and minimise the barriers to re-engaging with care, as well as prevent missed visits in the first place.

While the percentage of children lost to follow up in our cohort was relatively small, other studies do report a higher attrition [chapter 5]. Attrition is usually greater for children on pre-ART than for those on ART [chapter 4], which was also found within the adult population within the same clinic at Macha [59].
We suggest that our low attrition rates are due to an integrated package of care minimizing time spent at the clinic, a family-based clinic allowing guardians and children to come at the same review date, a patient tracking system, and the assumption that some children with difficult social circumstances receive appropriate (psychosocial) support and motivation to remain in care.

Available evidence continues to highlight the urgent need to improve retention rates for people enrolled in HIV treatment and care. To assist to launch tracing efforts at an early stage of lost to follow up, a system to facilitate the identification of patients that miss appointments is crucial [48]. Weak data management systems make it difficult for health care workers to identify when a patient is lost to follow up until long after she or he has missed an appointment. If a person is identified to be late for review, the next step of actual tracing can be very time and cost consuming. A large survey of pediatric HIV programs in Asia and sub-Saharan Africa [60] showed that, after a missed clinic visit, 83% of the sites utilized phone calls, 21% home visits by clinic staff, and 71% home visits by outreach workers. The majority (65%) of the 63 sites contributing data to this survey were in urban settings. In many of the rural settings phone network coverage is limited, which leaves out the option to contact clients by phone. Within our research setting each case of 'lost to follow up' was investigated to ascertain further details, in particularly if the child had died. Follow ups were done by one of the study assistants; an average of 2-4 children could be followed per day, travelling up to 155 kilometers, costing 120 US$ for transport costs only. These efforts and costs would be prohibitive within a normal clinic setting. Using community volunteers or outreach workers for contact tracing can be an acceptable alternative although this also requires good communication and feedback options, especially when dealing with a large catchment area and low population density.

To assess the long-term outcomes of ART in perinatally infected children as they age into adolescence, paediatric programmes in resource-limited settings will need to expand their focus beyond diagnosis and early monitoring to a chronic disease model [60]. Whether infected at birth or later in life, with prolonged survival, HIV-infected youth, caregivers, healthcare workers and teachers will be confronted with new challenges related to the long-term physical, psychological and

academic effects of HIV infection and treatment, as well as challenges associated with puberty and sexual activity.
Data on this group are limited, but issues as increasing self-responsibility, HIV related stigma and pressures from school or peers may contribute to poor adherence to treatment and disengagement from care.

Conclusion

HIV has proven to be a formidable challenge, but the tide is turning, also in Zambia. Even in countries that have reached high levels of service coverage, concerted efforts are needed to reach the most marginalized and vulnerable populations. Children living with HIV are some of the most vulnerable members of society. Each day that goes by almost 800 HIV-positive children die because of lack of access to treatment and care [9]. Ensuring their well-being and protecting their human rights is our shared responsibility.

There are many reasons why HIV care and treatment for infants and children lags behind that of adults. These challenges are complex and disparate, and can vary widely among regions, countries, and even individual health facility settings. Bottlenecks limiting paediatric treatment in resource-limited settings include poor access to diagnosis, weak systems for linkage to care and patient retention, few health centers and providers equipped to deliver paediatric ART, and drug regimens that are more complex to administer than adult regimens. Problems that are more pronounced in rural areas include high level of malnutrition among HIV-infected children, lack of health personnel, difficulties with transport of clients to the clinic, but also of drugs and diagnostics to the health facilities.
By identifying the barriers to a durable ART scale-up and treatment outcomes within a rural HIV program, the current analysis does not aim to provide an answer to all the complexities of rural HIV service delivery. Instead, it urges researchers towards continuous policy-relevant assessments of potential ways to overcome the cited barriers, and policy makers towards applying research-informed policy making and implementation in scaling-up ART in a high HIV-prevalence resource-limited setting. Our rural cohort illustrates that paediatric HIV service delivery in resource-limited settings is achievable. Additional attention to prompt diagnosis, early ART initiation, and active follow-up of children who miss appointments are urgent priorities for paediatric HIV programmes.

As perinatally-infected children reach adolescence, monitoring the long-term impact of HIV infection and ART will be critical to the success of treatment programs, including the ability of these programs to maintain viral suppression, immunologic function and normal physiologic processes, potentially impaired by long-term exposure to HIV and antiretroviral drugs. As more than 60% of the population in sub-Saharan Africa lives in rural areas [61], a large proportion of these HIV-infected youth will receive care and treatment in rural clinics and health centers. Future studies can provide critical information on these long-term treatment outcomes, as well as susceptibility to vaccine-preventable diseases, cognitive function and the sexual experiences of perinatally-infected youth, in a rural setting in sub-Saharan Africa.

With experience gained in implementing paediatric ART programs in sub-Saharan Africa over the past decade, innovative solutions to address and overcome these barriers have been developed. While these challenges impact most programs, the solutions are context-specific. Even though scientific analysis aims for generalizability and reproduction of proof, no 'one-size fits all' answers are available in the daily clinic setting. Programs need to determine the most appropriate solution for their setting. Individual review of the reality people live in –perceived or realistic-, in combination with compassion and empathy is what is needed.

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"Take the lead. Go for VCT."

Appendices

Appendix I

Nederlandse Samenvatting

De praktijk van rurale, paediatrische HIV-dienstverlening

Introductie

In dit proefschrift worden de gegevens van een samenwerking tussen verschillende partners gepresenteerd: Macha Research Trusts (voorheen Malaria / Medical Institute in Macha) en Macha Mission Hospital in Macha, Zambia; AIDSrelief Zambia en het Zambiaanse ministerie van volksgezondheid; Erasmus MC, Universitair Medisch Centrum Rotterdam, Nederland; en de Bloomberg School of Public Health, John Hopkins University, Baltimore, USA.
Macha Hospital is een van de 1,769 HIV/AIDS centra in Zambia [1]. Het ziekenhuis is uniek vanwege de langdurige goede samenwerking met de lokale gemeenschap en het aangrenzende onderzoeksinstituut, in ruraal Zambia.
De gegevens van het pediatrische HIV cohort die hun zorg ontvangt in dit rurale Zambiaanse ziekenhuis vormt de basis voor dit proefschrift. Hoewel de meeste studies naar HIV-geïnfecteerde kinderen in sub-Sahara Afrika worden uitgevoerd in stedelijke gebieden [2], waar de middelen en infrastructuur het best zijn, werden de studies in dit proefschrift uitgevoerd in een rurale gemeenschap in het kader van een observationele cohort studie van perinataal geïnfecteerde kinderen (PART studie, gestart in 2007). Hoewel onderzoek in een rurale omgeving een uitdaging is vanwege de beperkte middelen, geven deze studies inzicht in de gevolgen en de behandeling van HIV bij kinderen op lange termijn en de unieke barrières en uitdagingen met betrekking tot het verstrekken van zorg en behandeling in deze situatie.
In dit laatste hoofdstuk geven we een samenvatting van de gepresenteerde studies, inclusief de behaalde successen en resterende uitdagingen met betrekking tot pediatrische HIV-zorg in gebieden met beperkte middelen in ruraal sub-Sahara Afrika, en sluiten we af met een aantal toekomstperspectieven.

Samenvatting van de belangrijkste bevindingen

Deel 1 - Introductie

Na de algemene inleiding **[hoofdstuk 1]**, presenteren we een systematisch review van gepubliceerde gegevens over de werkzaamheid van antiretrovirale therapie in HIV-geïnfecteerde kinderen in sub-Sahara Afrika, hetgeen onze gegevens in een breder perspectief plaatst. Deze literatuurstudie, gepresenteerd in **hoofdstuk 2**, toont aan dat korte-termijn resultaten van HIV/ART behandelprogramma's in sub-Sahara Afrika veelbelovend zijn. Gezien de snelheid waarmee de uitbreiding van HIV/ART programma's heeft plaatsgevonden in de sub-Sahara regio, is het verkrijgen van gelijkwaardige resultaten in sub-Sahara Afrika programma's en Westerse landen een prestatie van formaat. De oudere leeftijd en verder gevorderd ziektestadium op het moment van start van behandeling van HIV-geïnfecteerde kinderen in sub-Sahara Afrika verhindert echter een directe vergelijkingen met kinderen in Westerse landen.

Late identificatie van HIV-geïnfecteerde kinderen ondersteunt de behoefte aan vroegere diagnose en behandeling. Betere toegang tot eenvoudig te gebruiken technologieën voor het diagnosticeren van HIV bij kinderen, het versterken van counseling en diagnostiek programma's, evenals PMTCT programma's, en herziene criteria, zodat kinderen in aanmerking komen voor ART in minder vergevorderde stadia van immuundeficïentie, zijn dringend nodig.
Meer dan de helft van de kinderen waren ondervoed bij aanvang van de behandeling. Dit vraagt om integrale modellen van zorg welke ondervoeding adresseren en zowel therapeutische en supplementaire voeding includeren.
Suboptimale antiretrovirale behandelingen waren gewoonlijk beschikbaar, slechts 63% van de studies meldde het gebruik van protease-remmers. Er is een duidelijke noodzaak voor een betere toegang tot pediatrische geneesmiddelen, inclusief vaste-dosis combinaties, en betere beschikbaarheid van effectieve tweedelijns medicijnen voor kinderen in sub-Sahara Afrika.
Gerapporteerde resultaten waren van behandelprogramma's geïmplementeerd in stedelijke centra. Continue belangenbehartiging is nodig voor betere toegang tot zorg voor HIV-besmette kinderen, met name in de rurale bevolking, met de noodzaak om deze programma's te monitoren en evalueren.
De literatuurstudie levert het bewijs dat behandelprogramma's in sub-Sahara Afrika effectief zijn in het leveren van virale suppressie, retentie van patiënten in zorg, en overleving, hetgeen bevestigt dat universele toegang tot behandeling een haalbare en essentiële prioriteit is. Aanvankelijke ART behandel resultaten tonen grote belofte voor de toekomst, maar er is geen ruimte voor zelfgenoegzaamheid. Er blijven nog veel obstakels over op de weg naar universele toegankelijkheid.

Deel twee - Barrières tot zorg en behandeling in ruraal Zambia

Een van de belangrijkste barrières tot toegang tot gezondheidszorg in ruraal sub-Sahara Afrika is de toegankelijkheid tot gezondheidsinstanties. Gebrek aan vervoer (54%), onvoldoende financiële middelen (60%) en slechte wegen (32%) waren vaak genoemde obstakels tot de toegang tot de kliniek, in deze rurale omgeving, in het bijzonder tijdens het regenseizoen **[hoofdstuk 3]**. De meerderheid van de zorgverleners liepen of fietsten naar de kliniek, en meer dan 25% van hen reisde meer dan 5 uur.
Openbaarmaking van de HIV status naar kinderen kwam niet vaak voor. Weinig kinderen, zelfs binnen de oudere leeftijdsgroepen, waren zich bewust van hun HIV status, met slechts 3% van alle kinderen die naar verluidt op de hoogte waren van hun HIV-infectie-status, en 17% van hen 10 jaar of ouder. Kinderen op ART hadden meer kans om bewust te zijn van hun status (33% versus 6%). De meerderheid van de zorgverleners vonden dat hun kind te jong was om hun HIV-status te weten, terwijl anderen bang waren om het hun kinderen te vertellen of niet wisten hoe dat te doen. Deze informatie werd gerapporteerd door de verzorger in plaats van het kind en kan een onderschatting zijn van het aantal kinderen met ware kennis van hun status, maar in ieder geval toont het de beperkte betrokkenheid van de zorgverlener in het proces van onthulling op dat moment.
Kinderen in ruraal Zambia hadden een aanzienlijke stijging in CD4+ T-cellen in het eerste jaar van ART en latere analyses van dezelfde cohort toonde aan dat twee jaar na de aanvang van ART deze toename in stand was gehouden. Gewichtstoename onder de HIV-geïnfecteerde kinderen die ART ontvangen in ruraal Zambia bereikten niet het niveau welke in andere delen van sub-Sahara Afrika gemeld wordt. Het zal nodig zijn strategieën te ontwikkelen om de toegang tot zorg en voeding te verbeteren om zeker te stellen dat er optimale, langdurige behandelingsresultaten zijn voor HIV-geïnfecteerde kinderen die woonachtig zijn in ruraal sub-Sahara Afrika.

Om te bepalen of de beperkte toegang (tot gezondheidsinstellingen) in rurale gebieden, welke te wijten is aan de specifieke uitdagingen voor zorgaanbieders en patiënten, van invloed is op de zorg en behandelingsresultaten, vergeleken we de kenmerken van kinderen met toegang tot HIV-zorg in stedelijke klinieken versus rurale klinieken op het moment van HIV kliniek registraties, de periode tot ART initiatie, en de respons op de behandeling **[hoofdstuk 4].** De meerderheid van zowel stedelijke als rurale kinderen presenteerden zich met ver gevorderde ziekte en ernstige mate van immunosuppressie. Een onverwacht bevinding, en in tegenstelling tot soortgelijke vergelijkingen van stedelijke, peri-urbane en rurale volwassenen, toonde kinderen in de stedelijke gebieden met verder gevorderde klinische en immunologische stadia van de ziekte.
Lange reisafstanden in de rurale gebieden zijn van invloed op de timing van kliniek bezoeken, evenals het beloop /attritie binnen het programma, met een hoog verlies-aan-follow-up onder kinderen die verder weg van de klinieken wonen, vooral onder kinderen die niet in aanmerking komen voor een behandeling. Zowel stedelijke als rurale kinderen reageerden goed op de behandeling, in overeenstemming met andere studies [hoofdstuk 2]. Het niveau van de immunologische en klinische respons werd beïnvloed door hun uiteenlopende uitgangskenmerken. Factoren die geassocieerd worden met een hoger risico op sterfte waren het bezoeken van een rurale kliniek, een jongere leeftijd, lagere WAZ, WHO graad 3 of 4, en lage (<5%) CD4 T-cel-percentage bij heb begin van ART. Echter, in een multivariate analyse bleek het bezoek aan een rurale kliniek niet langer significant geassocieerd met sterfte, terwijl de andere genoemde baseline-kenmerken dit nog wel waren. Mortaliteit was consistent hoger in rurale klinieken, mede door de jongere leeftijd en sterke mate van ondervoeding. Verlies in follow-up was hoger in de stedelijke kliniek en werd geassocieerd met dezelfde risicofactoren als mortaliteit. Het is mogelijk dat de hogere sterfte in de rurale gebieden deels kan worden verklaard door een succesvollere opsporing van personen en het confirmeren van de uitkomst.

Deel drie – Behandlings uitkomsten in ruraal Zambia

Aanvullend op de resultaten van de eerdere cross-sectionele analyse in de PART studie-cohort [hoofdstuk 3], bevestigde de studie van de behandel resultaten gedurende de eerste twee jaar van ART **[hoofdstuk 5]** dat ART effectief kan worden aangeboden in een rurale omgeving en toont het aan dat kinderen duurzame immunologische en virologische verbeteringen ervaren na het begin van ART. Vroege toenames in de CD4+ T-cellen percentages werden gedurende follow-up gehandhaafd.
De studie toont ook verbeteringen aan in de registratie en behandeling van kinderen op jongere leeftijd, welke betere klinische en immunologische karakteristieken hadden en minder ernstige stadia van progressie van de ziekte.
Samengevat, kinderen startten ART met een gemiddeld CD4 T-cel-percentage van 16,3% en hadden een aanvankelijke stijging van 1,8 procent per maand in de eerste 6 maanden van ART. Vervolgens verminderde de toename in CD4 T-cel percentages zich tot 0,23 procentpunt per maand. De meerderheid (82%) van de kinderen bereikten een CD4 T-cel percentage in het normale bereik (>25%) binnen het eerste jaar van ART. Therapietrouw van ART was hoog, met ongeveer 75% van de kinderen die >95% medicijn inname rapporteerden.
Toename in reistijd had een negatieve invloed op de waarschijnlijkheid van het bereiken van virale suppressie onder kinderen op ART, alhoewel, de meerderheid van de kinderen (87%) aanhoudende virale suppressie bereikte binnen de eerste twee jaar van de behandeling. Het waargenomen nadelig effect van lange reistijden op virussuppressie kan gevolgen hebben op ART behandeling in deze

omgeving. Als behandelprogramma's zich verder uitbreiden naar de rurale gebieden, dan zullen de kliniek behandelingsgebieden zich uitbreiden. Tenzij gedecentraliseerde modellen van zorg worden ingevoerd, zullen kinderen grote afstanden voor hun zorg en behandeling moeten blijven afleggen, hetgeen zowel hun vermogen om in de zorg te blijven en de response op de behandeling kunnen beïnvloeden.

Zoals in de eerdere analyse [hoofdstuk 4], in de rurale populatie werd een grotere mate van ondervoeding waargenomen in vergelijking met andere studies. In de studie die de groeipatronen **[hoofdstuk 6]** evalueerde van jonge HIV-geïnfecteerde kinderen met goede immunologisch herstel door ART in ruraal Zambia, is er een significante verbetering van zowel gewicht en lengte-voor-leeftijd na aanvang van ART. Verschillende patronen van de verbetering in de WAZ en HAZ werden gerelateerd aan respectievelijk ondervoeding en de leeftijd bij de aanvang van ART. Kinderen met ondergewicht ervoeren een grotere toename van de WAZ in de eerste 6 maanden van ART, en kinderen ouder dan 5 jaar bij aanvang ervoeren significant kleinere stijgingen van de HAZ per maand in vergelijking met kinderen jonger dan 2 jaar. Echter, een groot deel van de kinderen hadden ondergewicht (60%) en waren onvolgroeid (72%) bij het begin van ART en bleven ondergewicht behouden (45%) en onvolgroeid zijn(46%) na twee jaar behandeling, hoger dan waargenomen bij HIV-negatieve kinderen in dezelfde regio [3].
Dientengevolge, succesvolle behandeling met ART was niet in staat de effecten van HIV en ondervoeding op de groei volledig om te keren. Een samenwerking tussen HIV-behandeling en voedings programma's moet worden onderzocht, zodat kinderen een geïntegreerde zorg en behandelings aanpak ontvangen die ook voedingsondersteuning bevat. Verdere evaluatie van de invloed van voedsel suppletie op groei na ART initiatie is nodig.

Deel vier – Dienst verlening

De meerderheid van de kinderen die bij de HIV zorg en behandeling programma's aangemeld worden komen reeds in aanmerking voor ART op het moment van de registratie [hoofdstuk 4], zoals 60% van de kinderen in de studie, waar gekeken werd naar sterftecijfers en klinische indicatoren van sterfte in de periode voorafgaand aan de start van ART **[hoofdstuk 7].** Hoewel de sterftecijfers verschillen tussen programma's, afhankelijk van de populatie karakteristieken en de striktheid in het vaststellen van de sterfgevallen, geven schattingen aan dat een aanzienlijk deel van de kinderen die de zorg binnenkomen overlijden voordat ze met ART beginnen. In deze studie was de cumulatieve mortaliteit voor ART initiatie 13,3% hetgeen vergelijkbaar was met de cumulatieve mortaliteit van 14,4% onder kinderen na ART initiatie in deze pediatrische cohort [hoofdstuk 5]. Daarnaast is de sterfte in de eerste drie maanden na start in de studie onder kinderen die in aanmerking komen voor ART vergelijkbaar met de sterfte in de eerste drie maanden na ART initiatie (ongepubliceerde gegevens). Factoren die samenhangen met sterfte in deze studie zijn: jongere leeftijd, bloedarmoede en lagere WAZ score bij studie opname en deze waren vergelijkbaar onder kinderen die in aanmerking komen en niet in aanmerking komen voor ART bij studie opname.
Dit sterftecijfer blijft onaanvaardbaar hoog in de context van ART, en mortaliteit van kinderen met HIV draagt aanzienlijk bij aan de totale kindersterfte, vooral in landen met een hoge ziekte-last. De voordelen voor kinderen op ART moet dezelfde zijn in een onbemiddelde als in bemiddelde omgeving, maar het sterftecijfer onder de eerste is acht keer hoger dan die van de laatste [4]. Dit onderstreept de noodzaak om de inspanningen te verhogen om HIV-geïnfecteerde kinderen te identificeren op jongere leeftijd en in vroeg stadium van de ziekte, zodat ze zich kunnen registreren

voor HIV zorg en behandeling programma's voorafgaand aan het in aanmerking komen voor ART. Op deze manier kunnen zij en hun familie voorbereid worden om de levenslange therapie te beginnen en de volledige voordelen van de behandeling te ontvangen.

Antiretrovirale behandeling (ART) opties voor jonge kinderen met gelijktijdige infectie met HIV en tuberculose zijn beperkt in omgevingen met weinig hulpmiddelen vanwege beperkte gegevens over het gebruik van efavirenz (EFV). Bijgevolg is er een behoefte aan alternatieve behandelingsstrategieën voor jonge kinderen met tuberculose en gegevens om deze te ondersteunen. Gezien de beperkte antiretrovirale behandeling opties in deze settings voor kinderen die rifampicine ontvangen, en de noodzaak om ART zo spoedig te starten om een toename van ziekte en sterfte te voorkomen, werd er een EFV doseringsschema ontwikkelt, geëxtrapoleerd uit beschikbare farmacokinetische gegevens, voor de klinische zorg van jonge kinderen co-besmet met tuberculose. Dit doseringsschema werd geïmplementeerd als de standaard van zorg bij Macha Hospital in de Zuiderlijke Provincie van Zambia en was onafhankelijk van de observationele cohort studie. Behandelingsresultaten van kinderen jonger dan 3 jaar of die minder wegen dan 10 kg, die of EFV-based ART plus anti-tuberculeuze behandeling of nevirapine-based (NVP) ART ontvingen werden vergeleken **[hoofdstuk 8].**
Ondanks de slechtere gezondheid tijdens de initiatie van ART, vertoonden kinderen jonger dan 3 jaar die werden behandeld voor tuberculose en een EFV-based ART regiment kregen significante verbeteringen in de klinische, immunologische en virologische resultaten, in vergelijking met jonge kinderen die een NVP-gebaseerd regiment ontvingen. Gezien het toenemende aantal jonge HIV-geïnfecteerde kinderen die beginnen met ART in sub-Sahara Afrika, de hoge ziektelast van tuberculose, de beperkte behandelingsmogelijkheden in deze regio, en de beperkte virologische effectiviteit van NVP, kan gebruik van EFV bij jonge kinderen worden overwogen. Dit is de eerste studie die toont dat EFV effectief kan worden toegepast bij jonge HIV-geïnfecteerde kinderen met tuberculose. Aanvullende studies zullen nodig zijn om een EFV dosering strategie voor jonge kinderen gecoinfecteerd met tuberculose te valideren en te optimaliseren.

In hoofdstuk 2 hebben we aangetoond dat reisafstand en reistijd belemmeringen zijn voor de zorg voor HIV-besmette kinderen in onbemiddelde omgevingen. Decentralisatie wordt voorgesteld als zijnde een van de sleutels tot het opschalen van toegang tot antiretrovirale behandeling, en in **hoofdstuk 9** hebben we een dergelijk programma geevalueerd door de behandelingsresultaten te vergelijken voor kinderen die zorg ontvangen middels mobiele en ziekenhuis-gebaseerde HIV-klinieken in ruraal Zambia. We zagen dat, ondanks vergelijkbare klinische en immunologische resultaten, kinderen in de outreach-groep minder kans toonden op virologische onderdrukking. Dit zou kunnen komen door een lagere therapietrouw. Continue aandacht voor de kwaliteit van de geleverde diensten en het belang van therapietrouw is van cruciaal belang voor het succes van decentrale zorg.

De ongelijkheid in toegang tot behandeling voor kinderen en volwassenen is groot aangezien de verstrekking van ART voor kinderen unieke obstakels heeft. Meerdere uitdagingen zijn geïdentificeerd, en voorbeelden van lokaal aangepaste strategieën om deze te overwinnen zijn gedocumenteerd. **Hoofdstuk 10** beoordeelt de haalbaarheid en effectiviteit van pediatrische ART in sub-Sahara Afrika, en toont enkele van de succesvolle manieren en ontwikkelingen in de dienstverlening en zorg. Knelpunten die vooral van invloed zijn op kinderen en die pediatrische

behandeling beperken worden in dit hoofdstuk besproken, met inbegrip van een tekort aan goed opgeleide zorgverleners, onvoldoende laboratoriumcapaciteit voor diagnose en monitoren van behandeling bij kinderen, therapietrouw, kennis van HIV-infectie status en retentie in de zorg. Het adresseren van personeels tekorten is essentieel voor de uitbreiding van pediatrisch ART-programma's, met name in rurale gebieden. Om de toegang tot ART te vergroten, beveelt WHO aan tot het verschuiven van taken, waarbij een niet-gespecialiseerd kader verantwoordelijkheden op zich neemt in ART management[5]. Veel programma's implementeerden een of andere vorm van taakverschuiving, resulterend in een vermindering van de programma kosten en het verhogen van de efficiency van het programma. Echter, supervisie en begeleiding zijn van belang om een hoge kwaliteit van zorg te waarborgen (zie ook hoofdstuk 9).

Klinische laboratoria spelen een cruciale rol in de zorg en behandeling van HIV-geïnfecteerde kinderen. De noodzaak om laboratorium capaciteit uit te breiden en om eenvoudige, goedkope point-of-care testen voor diagnose bij kinderen en het monitoren van viral-load te ontwikkelen is erkend en hierboven beschreven.

Consistente toepassing van doseringsrichtlijnen door zorgverleners en patiënten is essentieel om de kans op falen van de behandeling te verminderen door onderdosering of van toxiciteit door overdosering. Bij kinderen is het juist doseren moeilijker aangezien het afhangt van monitoren van de groei door middel van accurate gewicht en lengte bepaling. Veel programma's hebben innovatieve strategieën geïmplementeerd voor de verbetering van pediatrische therapietrouw, in additie tot de aanbevolen informatie verstrekking voor verzorgers door middel van compliance-counseling. Dit omvat het inschakelen van behandeling supporters; trainen van personeel in het meten van pediatrische therapietrouw; het identificeren van betrouwbare, eenvoudige technologie en betaalbare methoden ter beoordeling de therapietrouw; implementeren van een gezinsgerichte aanpak; het aanbieden van groeps- en psychosociale begeleiding voor verzorgers en kinderen; aanbieden van compliance herinneringen, en het aanbieden van training in behandeling ervaring.

De relatie tussen de bekendmaking van de HIV status en therapietrouw wordt erkend en de WHO beveelt aan dat kinderen ouder dan 10 jaar deelnemen aan discussies over hiv-testen [6] Echter, uit onderzoek blijkt dat het openbaren van de HIV status niet algemeen verbreid is in sub-Sahara Afrika. Formele richtlijnen en aanbevelingen inzake de informatieverstrekking aan kinderen, alsmede opleiding van zorgverleners en counselors die dit proces begeleiden zijn nodig om het niveau van openbaarmaking onder kinderen in sub-Sahara Afrika te verhogen.

Zoals voor de therapietrouw is retentie in de zorg ingewikkelder voor kinderen dan voor volwassenen. Bijgevolg moeten strategieën om retentie te verbeteren rekening houden met de behoeften en motivatie van zowel het kind als de verzorger. Een familie-gecentreerde benadering, gedecentraliseerd model van de zorg, en een home-based model van zorg zijn enkele van de modellen die zijn geïmplementeerd om retentie van de patiënt te verbeteren.

Een deel van de toekomstige uitdagingen voor de peadiatrische programma's die werden geïdentificeerd omvatten ondermeer een familie-gecentreerde benadering, de invoering van elektronische medische dossiers systemen, en toereikende financiering.

Toekomst perspectieven

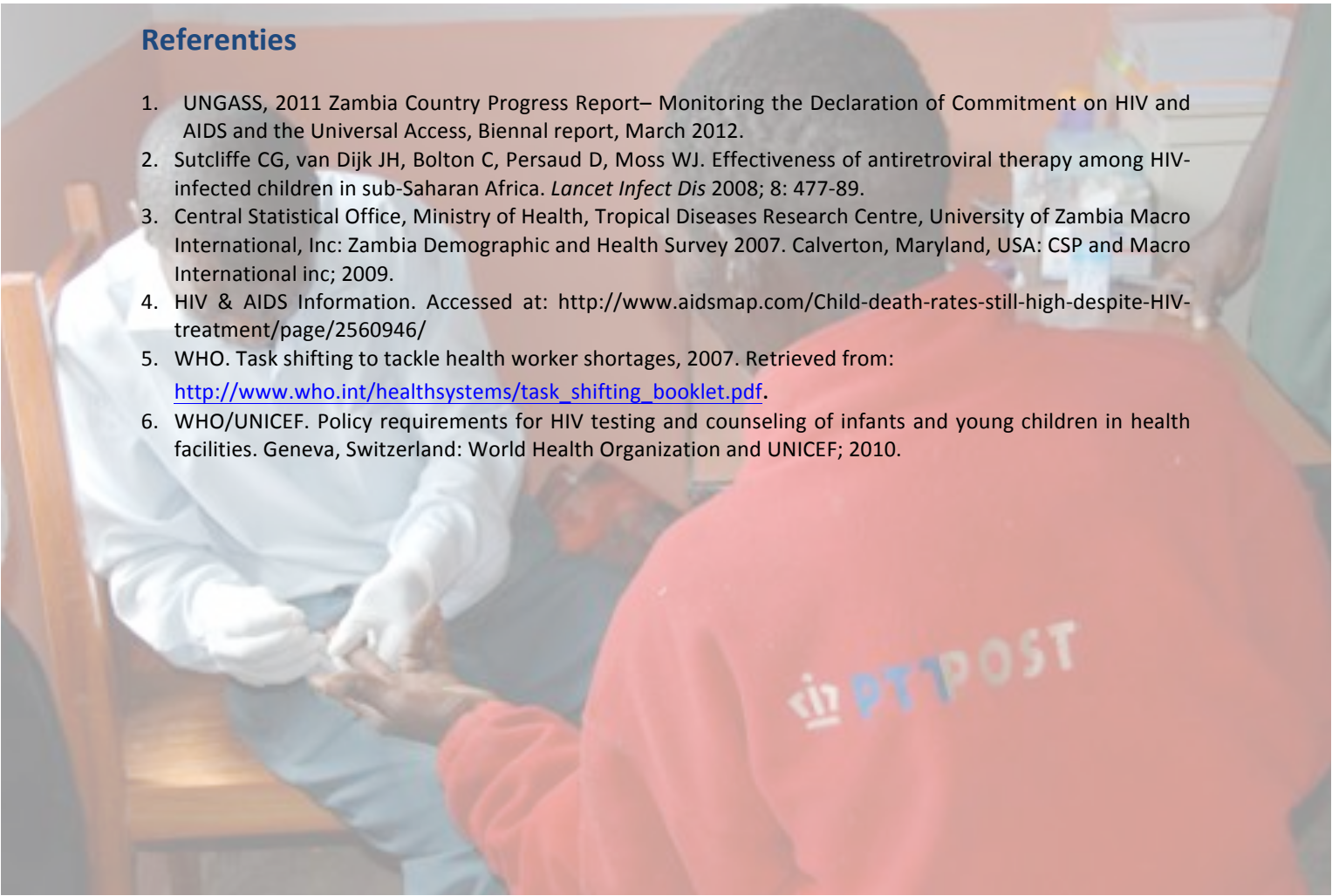
Het doel van dit proefschrift is om de kenniskloof te overbruggen die momenteel bestaat in ruraal sub-Sahara Afrika met betrekking tot de barrières tot gezondheidszorg, ziekteprogressie en behandelingsresultaten van HIV-geïnfecteerde kinderen. Aangezien veel HIV-geïnfecteerde kinderen

in ruraal sub-Sahara Afrika wonen, geven deze studies inzicht in de unieke barrières en uitdagingen die samenhangen met het verstrekken van zorg en het geven van behandeling in deze situatie, en mogelijke oplossingen, zodat de lange termijn gezondheid en welzijn van deze kinderen en jongeren kan worden bereikt.

Kinderen in sub-Sahara Afrika reageren even goed op de behandeling als kinderen in het Westen. Het grote verschil in de uitkomsten is het gevolg van zowel biomedische als programma factoren en omvat een ernstiger ziektestadia bij diagnose, andere co-infecties, ondervoeding en uitstel in het starten van ART.

Echter, de uitdagingen om de HIV-epidemie onder kinderen te beteugelen in ruraal sub-Sahara Afrika zijn nog steeds enorm. Manieren voor een verdere verbetering van de toegankelijkheid van de zorg en het zekerstellen van langdurig optimale behandeluitkomsten voor HIV besmette kinderen in ruraal sub-Sahara Afrika in de (nabije) toekomst, kunnen worden onderverdeeld in:

1. Het verbeteren van vroege identificatie van aan HIV-blootgestelde kinderen en toegang tot vroegtijdige zuigeling diagnose (PMTCT, connectie, point-of-care diagnostiek);
2. Ondersteuning voor de uitbreiding van ART-programma's naar rurale gebieden om de toegankelijkheid tot behandeling te verhogen en onrechtvaardigheden te doen verminderen (doelstellingen, integratie, decentralisatie, taakverschuiving);
3. Geïntegreerde aanpak van HIV zorg en behandeling met voedingsondersteuning;
4. Zorgoptimalisering om immunologische en virologische verbeteringen te behouden (disclosure, therapietrouw, toegang tot optimale behandeling regimes en monitoring)
5. Het verbeteren van de retentie in zorg



Referenties

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Appendix II

Acknowledgements

The success of any research depends largely on the encouragement and guidelines of many others. I take this opportunity to express my gratitude to the people who have been instrumental in the successful completion of this thesis.

First and foremost I would like to express my deep gratitude to *all children and their caregivers* enrolled in the Macha HIV clinic, who have unselfishly contributed to this work with their time and inputs. Much of what I have learned came as a result of providing care and treatment to these wonderful children. In their own ways, they inspired me and subconsciously contributed a tremendous amount of motivation and relevance to this work, and content to this thesis.

I wish to express my gratitude to *Dr. Jan Nouwen*, for being instrumental in initiating and establishing the collaboration between Erasmus MC in the Netherlands and Macha Research Trust in Zambia. His willingness to motivate me and propose me as PhD candidate contributed greatly to this work. I am grateful to Jan for his patient guidance and enthusiastic encouragement during my research work, for his useful and constructive recommendations during the write up of this thesis, for proof reading the manuscript and making valuable comments and suggestions.

I am highly indebted to the departments Medical Microbiology & Infectious Diseases and Virology at Erasmus MC that offered me the PhD fellowship, and for their support in completing this work. With special thanks to *Prof. Dr. Henri Verbrugh* and *Prof. Dr. Charles Boucher*.

My deepest gratitude also due to my co-Principal Investigator in the PART study, *Dr. William Moss*, for the pleasant collaboration we had over the years. His professional guidance and valuable support during the planning and development of this research work have been inspiring. His useful critiques during manuscript writing have taught me much.

I am grateful to *Dr. Phil Thuma*, for following his dream to work towards reducing the burden of malaria within his area of influence. For introducing me to the 'world of research' and allowing the research institute to broaden its focus with our current work in HIV.

I would like to gratefully acknowledge *Dr. Catherine Sutcliff* with whom I had the pleasure of working with on the PART study, and who provided the invaluable statistical support for this study. I will miss our discussions and manuscript write-ups.

My heartfelt thanks goes to the *PART study team* for their cooperation in carrying out the research work, without whose assistance this study would not have been successful. Thanks to their kindness towards the study participants, and their perseverance over the years. They sincerely devoted their time and service to every activity and task that was required within this research.

I thank the *Research institute and Macha hospital* for providing an authentic environment and facilities to work from.

The continuous support from our support team at home: *Mrs. Moono Chali, Mrs. Dorothy Nsemu, Mr. Elima Nakubiana and Mr. Felix Malumane,* enabled me to take up my tasks at the research institute and the hospital. Their interest in the work and our daily communication provided insights in the local culture that helped our family to live and work in this small rural village called Macha for many years. Their love and efforts made us feel at home.

I am grateful to my dear *Macha friends and colleagues* for being the surrogate family during the many years we lived in Macha, and for their continued moral support.

Finally, yet importantly, I would like to thank my beloved *parents* for their blessings, and my *friends* for their help and wishes for the successful completion of this project. Great thanks go to my *beloved family* for their understanding and support to me in completing this work. An honorable mention goes to *Gertjan*, who inspired, encouraged and fully supported me in every step on the way.

Ada, for having been in my life as my eldest sister, and being a light in many ways. For introducing me to Macha, where much of this work is based upon.

To *Jehovah-Jireh*, I am thankful for the strength that keeps me standing and for the hope that keeps me going.

I am standing on the shoulders of the ones who came before me
I am stronger for their courage, I am wiser for their words
I am lifted by their longing for a fair and brighter future
I am grateful for their vision, for their toiling on this earth

We are standing on the shoulders of the ones who came before us
They are saints and they are humans, they are angels, they are friends
We can see beyond the struggles and the troubles and the challenge
When we know that by our efforts things will be better in the end

I am standing on the shoulders of the ones who came before me
I am honored by their passion for our liberty
I will stand a little taller, I will work a little longer
And my shoulders will be there to hold the ones who follow me

By Joyce Johnson Rouse

Appendix III

Curriculum Vitae

Janneke van Dijk was born in Zwollerkerspel, the Netherlands, being the 4th daughter in a family of 5 girls. After graduating from secondary school (Meander College in Zwolle), she started her medical training as theatre nurse at 'the Venderink' in Hengelo. During this 3-year program, she did her in-service training at the Juliana Hospital in Apeldoorn. She graduated in 1988 and continued to work at the same hospital to gain more experience in the different fields of surgery. During the years 1989-1990, she worked as a theatre-nurse at the Triemli Spital in Zurich, Switzerland, with a focus on Cardiac surgery.

A visit to her elder sister Ada van Dijk, who worked as a midwife at Macha Hospital in Zambia, made her heart tick for Africa and enthusiastic about the option to work in a developing country. Change of profession was preferred, and Janneke enrolled in medical school at the Erasmus University in 1990. During this period, she did her surgery elective at the Verwoerd Hospital in Pretoria, South Africa. She participated in an elective in tropical medicine in Queens Hospital in Blantyre and Phalomo Hospital in Malawi, as well as in a research elective at the Maryland University in Baltimore, the USA. In 1996, she obtained her medical degree and started her residency in surgery, which she did at the Haven Ziekenhuis in Rotterdam. Her residency in Obstetrics and Gynecology she did at the IJsselland Ziekenhuis in Capelle aan de Ijssel. She graduated her training in Tropical Medicine at the School of Public Health (NSPH in Utrecht) in 1999.

In 2000, she worked as a short-term volunteer doctor and instructor at a rural health clinic near Hyderabad, India. After her first child (Merel Teresa) was born, she went to work as a resident doctor at Murambinda Hospital in rural Zimbabwe. There she worked for 2 years, gaining experience in the diversity of pathology seen at a rural African hospital and experiencing the devastation of HIV when no treatment was available. After the birth of her second child (Elmo Boaz, 2003) the family went and settled in Macha, Zambia, where she worked as residential doctor and research associate, later becoming the Clinical Research Director of the Macha Research Trust. It is during these years that collaboration was started between the Erasmus University at Rotterdam, and the Research Institute at Macha. Several student and staff exchanges, capacity building programs, and research projects were initiated and completed, with a primary focus on HIV and Tuberculosis. In 2008, she was offered a PhD fellowship at the department of Medical Microbiology & Infectious Diseases and the department of Virology, which provided a platform for further capacity building, dissemination of results, and the construction of this thesis.

Appendix IV

List of Publications

van Dijk J, Hachaambwa L, Mulenga M, Thuma P.
Response of hemoglobin concentration to oral supplemental iron in children living in a malaria endemic area of Zambia. *Med J Zambia* 2007; 34:86-91

Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss W J.
Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. *Lancet Infect Dis* 2008; 8:477-89

van Dijk JH, Sutcliffe CG, Munsanje B, Hamangaba F, Thuma PE, Moss WJ.
Barriers to the care of HIV-infected children in rural Zambia: a cross-sectional analysis. *BMC Infectious Diseases* 2009; 9:169

Nyunt MM, Adam I, Kayentao K, van Dijk J, Thuma P, Mauff K, Little F, Cassam Y, Guirou E, Traore B, Doumbo O, Sullivan D, Smith P, Barnes KI.
Pharmacokinetics of Sulfadoxine and Pyrimethamine in intermittent preventive treatment of malaria in pregnancy. *Clin Pharmacol Ther* 2010; 87(2): 226-34

Sutcliffe CG, Bolton-Moore C, van Dijk JH, Cotham M, Tambatamba B, Moss WJ.
Secular trends in pediatric antiretroviral treatment programs in rural and urban Zambia: a retrospective cohort study. *BMC Pediatrics* 2010; 10:54

Verweij KE, Kamerik AR, van Ingen J, van Dijk JH, Sikwangala P, Thuma P, Nouwen JL, van Soolingen D. **Application of modern microbiological diagnostic methods for tuberculosis in Macha, Zambia.** *Int J Tuberc Lung Dis* 2010; 14(9): 1127 – 1131

Thuma PE, van Dijk J, Bucala R, Debebe Z, Nekhai S, Kuddo T, Nouraie M, WeissG, Gordeuk VR.
Distinct Clinical and Immunologic Profiles in Severe Malarial Anemia and Cerebral Malaria in Zambia. *J Inf Dis* 2011; 203: 211-219

Sutcliffe CG, van Dijk JH, Munsanje B, Hamangaba F, Sinywimaanzi P, Thuma PE, Moss WJ. **Weight and height z-scores improve after initiating ART among HIV-infected children in rural Zambia: a cohort study.** *BMC infectious Diseases* 2011; 11:54

van Dijk JH, Moss WJ, Sutcliffe CG.
Feasibility and Challenges in Providing Antiretroviral Treatment to Children in Sub-Saharan Africa. *Current Pediatric Reviews* 2011; 7, 154-165

van Dijk JH, Sutcliffe CG, Munsanje B, Sinywimaanzi P, Hamangaba F, Thuma PE, Moss WJ. **HIV-infected children in rural Zambia achieve good immunologic and virologic outcomes two years after initiating HAART.** *PloS ONE* 2011; 6(4): e19006.

Sutcliffe CG, van Dijk JH, Munsanje B, Hamangaba F, Siniwymaanzi P, Thuma PE, Moss WJ. **Risk factors for pre-treatment mortality among HIV-infected children in rural Zambia: a cohort study.** *PLoS ONE* 2011; 6(12): 329294.

Estopinal CB, van Dijk JH, Sitali S, Stewart H, Davidson MA, Spurrier J, Vermund SH.
Availability of Volunteer-Led Home-Based Care System and Baseline Factors as Predictors and Clinical Outcomes in HIV-infected Patients in Rural Zambia. *PloS ONE* 2012; 7(12): 249564

van Dijk JH, Sutcliffe CG, Hamangaba, H, Bositis B, Watson DC, Moss WJ.
Effectiveness of efavirenz-based regimens in young HIV-infected children treated for tuberculosis: a treatment option for resource-limited settings. *PLoS ONE* 2013; 8(1): e55111

Nichols BE, Boucher CAB, van Dijk JH, Thuma PE, Nouwen JL, Baltussen R, van de Wijgert J, Sloot PMA, van de Vijver DAMC.
Cost-effectiveness of Pre-Exposure Prophylaxis (PreEP) in preventing HIV-1 infections in rural Zambia: a modeling study. *PLoS ONE* 2013; 8(3): e59549

Comfort AB, van Dijk JH, Mharakurwa S, Stillman K, Gabert R, Korde S, Craig A, Nachbar N, Derriennic Y, Musau S, Hamazakaza P, Zyambo KD, Zyongwe N, Hamainza B, Thuma PE.
Hospitalizations and costs incurred at the facility level following the scale-up of malaria control: pre-post comparisons from two hospitals in Zambia. *<submitted to AJTMH>*

Comfort AB, van Dijk JH, Mharakurwa S, Stillman K, Hathi P, Korde S, Craig AS, Nachbar N, Derriennic Y, Gabert R, Thuma PE.
Malaria Control in Rural Zambia and its Effect on Pediatric Blood Transfusions: A Time Series Analysis. *<submitted to Malaria Journal>.*

Van Dijk JH, Moss WJ, Hamangaba F, Munsanje B, Sutcliffe CG.
Scaling-up access to antiretroviral therapy for children: care and treatment at mobile and hospital-based HIV clinics in rural Zambia. *<submitted to BMC Health Services Research>.*

Appendix V

PhD portfolio

Name PhD student	Janneke H. van Dijk
Erasmus MC department	Department of Medical Microbiology & Infectious Diseases, Department of Virology
PhD period	2008-2013
Promotor	Prof.dr. HA. Verbrugh, Prof. dr. C. Boucher
Copromotor	Dr. JL Nouwen, Dr. WJ Moss

Summary of PhD training activities

General academic and research skills

Pediatric HIV training, Ministry of Health (MoH) Zambia, Lusaka, Zambia - 2008
Principles of Research in Medicine and Epidemiology, Nihes, Rotterdam, Nl - 2009
Introduction to Data-analysis (ESP03), Nihes, Rotterdam, Nl- 2009
1st Annual Pediatric Palliative Care Symposium, MoH Zambia / EGPAF, Lusaka, Zambia - 2011
Mobile Health without Borders, online course Stanford University - 2013

Selection of Conferences and presentations

2008

- 39th Union World Conference on Lung Health
  16-20 October 2008, Paris, France
  Poster presentation: The added value of introducing sputum culturing in diagnosing tuberculosis rural Zambia

2009

- 3rd International Workshop on HIV Treatment, Pathogenisis and Prevention Research in Resource Limited Settings, INTEREST
  26-29 May 2009, Lusaka, Zambia
  Oral presentation: Characteristics of HIV-infected Children Attending an HIV Clinic in Rural Zambia
- 1st International Workshop on HIV Pediatrics
  17-18 July 2009, Cape Town, South Africa
- 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention
  19-22 July 2009, Cape Town, South Africa
- National Health Research Conference and Symposium on Non-Communicable Diseases.
  28-30 September 2009, Lusaka, Zambia

Oral presentation: Barriers to the Care of HIV infected Children in Rural Zambia: a Cross-sectional Analysis.

Oral presentation: Differences in presentation, treatment initiation and response to antiretroviral therapy among HIV-infected children in urban and rural Zambia: a retrospective cohort study.

2010

- 17th Conference on Retroviruses and Opportunistic Infections
  16-19 February 2010, San Francisco, USA
  Poster presentation: The potential impact of recent infections, HIV testing and start of antiretroviral drugs at a CD4 of <350 on the HIV epidemic in a rural area in Zambia: a mathematical model
- 2nd International Workshop on HIV pediatrics
  16-17 July 2010, Vienna, Austria
  Poster presentation: Time to treatment initiation and pre-HAART mortality among HIV-infected treatment-naïve children in rural Zambia
  Poster presentation: Shorter travel times are associated with better treatment outcomes among HIV-infected children receiving care in rural Zambia.
- XVIII International AIDS Conference (AIDS 2010)
  18-23 July 2010, Vienna, Austria
  Poster presentation: Challenges in the PMTCT cascade in rural Zambia: evaluation of a PMTCT program and call for holistic approach
  Poster presentation: Low retention rate of pre-ART HIV infected patients after successful early enrolment in HIV care, a rural Zambian experience

2011

- 5th International Workshop on HIV Treatment, Pathogenisis and Prevention Research in Resource Limited Settings, INTEREST
  10-13 May 2011, Dar es Salaam, Tanzania
  Oral presentation: point-of-care device to measure lactate levels in HIV patients in rural Zambia; association with d4T-based regimen but no severe hyperlactatemia found
  Oral presentation: Effectiveness of AFV-based ART regimens in young children requiring TB/HIV co-treatment: a possible treatment option for resource-limited settings?
  Poster presentation: Intensive Tuberculosis screening in HIV infected persons not yet on Antiretroviral Treatment, in Macha, rural Zambia
  Poster presentation: Working towards universal testing: coverage and acceptance of mobile voluntary counseling and testing in a rural African setting

2012

- 6th International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource Limited Settings, INTEREST
  8-11 May 2012, Mombasa, Kenya
  Poster presentation: Unmet need for contraception in people living with HIV attending a rural HIV clinic in Zambia

- Grenzenloos Symposium
  26 Jun 2012, Rotterdam, the Netherlands.
  Oral presentation: Rural realities in ART roll out
- 4th International Workshop on HIV Pediatrics
  20-21 July 2012, Washington DC, USA
  Poster presentation: Turnaround times for early infant diagnosis of HIV infection in rural southern Zambia
- XIX International AIDS Conference
  22-27 July 2012, Washington DC, USA
  Poster presentation: Effectiveness of EFV-based ART regimens in young children requiring TB/HIV co-treatment: a possible treatment option for resource-limited settings
  Oral poster presentation: Scaling-up access to antiretroviral treatment: a comparison of outcomes among HIV-positive children receiving treatment at mobile and hospital-based HIV clinics in rural Zambia.

Continuing Medical Education

- HIV Clinicians' Meeting
  Zimbabwe HIV Clinicians society, 18 May 2013, 7 CPD point
- 2011 State of the ART series: Improving HIV Treatment Approaches
  Medscape, 14 Jan 2013, credit 2.00
- HIV Workforce and New Models for HIV Care: An Expert's Perspective
  Medscape, 10 Jan 2013, credit 0.75
- The Role(s) of ART in Preventing HIV – New Data and New Approaches
  Medscape, 4 Jul 2011, credit 1.50
- Understanding Zoster: Impact on the Individual and on Society
  Medscape, 3 July 2011, credit 0.50
- Video-Based HIV Counseling Increases HIV testing in Teens
  Medscape, 6 May 2011, credit 0.25
- HIV Basics (Part 1) course
  Global Health e-Learning Center, 27 May 2011
- Fewer Missed HIV Diagnoses: Cases with Patient Communication Videos
  Johns Hopkins Continuing Medical Education, 22 Feb 2011, credit 1.25
- Couples Therapy Reduces Risk in HIV-Serodiscordant Couples
  Medscape, 13 October 2010, credit 0.25
- Early Antiretroviral Therapy Cuts HIV-Related Mortality by 75%
  Medscape, 11 October 2010, credit 0.25
- Controversies in HIV: Management of the Treatment-Naïve Patient
  Medscape, 2 June 2009, credit 0.50

Supervising Research Electives

2008

Application of modern microbiological diagnostic methods for Tuberculosis in Macha, Zambia

Arianne Kamerik, Evelyne Verweij – EUR School of Medicine, Erasmus MC, the Netherlands (18 Mar – early Aug 2008)

Impact of Community Support on HIV/AIDS Outcomes in Rural Zambia

Christopher Estopinal - Vanderbilt University School of Medicine, USA (May-Jul 2008)

Lactate levels, drug- resistance and mortality in HIV clinic population in Macha, rural Zambia

Reshmie Ramautarsing - EUR School of Medicine, Erasmus MC, the Netherlands (10 Nov 2008 – late Feb 2009)

2009

Tuberculosis in HIV-infected children in rural Zambia - an epidemiological field study

Denis Kleinknecht, Medizinischen Universität Innsbruck, Germany (Jul – Sep 2009)

Prevention of Mother to child transmission of HIV: Evaluation of PMTCT program in a rural hospital in Zambia

Jolande Zijlstra, Bsc - Master's student International Public Health, Vrije Universiteit Amsterdam (8 April – 6 Aug 2009)

Prevalence of bacterial pathogens and antibiotic resistance patterns in patients admitted with a suspected bacterial infection in a rural hospital in Zambia

Fleur Bolders, Dionne Jakoba - laboratory technician students, Hoge school Rotterdam, the Netherlands (7 Feb – 6 May 2009)

Outcomes of 3½ years of follow up in HIV positive patients in rural Zambia: a retrospective study

Johan Janssen, Mark van Treijen – EUR School of Medicine, Erasmus MC, the Netherlands (12 March - 12 June 2009)

Lactate levels, drug- resistance and mortality in HIV clinic population in Macha, rural Zambia (continuation)

Niels Bech, Wouter Hogendoorn - EUR School of Medicine, Erasmus MC, the Netherlands (17 Sept – 21 Nov 2009)

2010

Intensive Tuberculosis screening in HIV infected persons not yet on Antiretroviral Treatment, in Macha, rural Zambia

Rachel van Eersel, Manon Kalle (6 March – 2 Aug 2010)

Fleur de Vries (13 Sept 2010 – 28 Feb 2011)

Marit van Mourik (17 Dec 2010 – 18 Mar 2011)

2011

Intensive Tuberculosis screening in HIV infected persons not yet on Antiretroviral Treatment, in Macha, rural Zambia (continuation)

Viola Kraak, Geeske Brouwer (7 March – 18 July 2011)

Marit van Mourik (27 July – 26 Sept 2011)

Lidewij de Vries (22 Sept 2011 – 28 Feb 2012)

An overview of the PMTCT program in Macha, rural Zambia (May 2009 – Dec 2010)

Viola Kraak, Geeske Brouwer (7 March – 18 July 2011)

Julie van Buitenen (25 July-26 Aug 2011)

Unmet need for contraception in people living with HIV attending a rural HIV clinic in Zambia

Maaike Helmer (4 July-5 Aug 2011)

Tino Lindner (29 Sept – 30 Nov 2011)

2012

Intensive Tuberculosis screening in HIV infected persons not yet on Antiretroviral Treatment, in Macha, rural Zambia (continuation)

Gemmeke Hagoort (1 Feb – 30 April 2012)

Appendix VI

Abbreviations

ABC	Abacavir
AIDS	Acquired Immune deficiency syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Treatment
ARV	Antiretroviral
AZT	Zidovudine
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and prevention
CI	Confidence interval
D4T	Stavudine
DBS	Dried blood spots
DNA	Deoxyribonucleic acid
EFV	Efavirenz
EID	Early Infant Diagnosis
EDTA	Ethylenediaminetetraacetic acid
FDC	Fixed-dose combination
HAART	Highly active antiretroviral therapy
HAZ	Height-for-age z-score
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IQR	Interquartile range
LPV/r	Lopinavir/ritonavir
LTFU	Lost to follow up
MCH	Maternal and Child Health
NRTI	Nucleoside reverse transcriptase inhibitors
NVP	Nevirapine
PEPFAR	President's Emergency Plan for AIDS Relief
PCR	Polymerase chain reaction
PMTCT	Prevention of Mother to Child Transmission
PY	Person-years
RNA	Ribonucleic acid
SAS	Statistical analysis system
Sd	Single dose
SD	Standard deviation
SES	Socio-economic status
SSA	Sub-saharan Africa
3TC	Lamivudine
UNAIDS	United Nations program on HIV/AIDS
USD	United States dollar

WAZ	Weight-for-age z-score
WHO	World Health Organization
ZMK	Zambian Kwacha