Outcomes and effectiveness of antiretroviral therapy for HIV-infected children in Southern African treatment cohorts.

By

Mary-Ann Davies

Thesis presented for the degree of

Doctor of Philosophy

In the School of Public Health and Family Medicine

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Supervisors: Associate Professors Andrew Boulle and Brian Eley

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

Mary-Ann Davies

May 2013

ABSTRACT

Since 2004, increasing numbers of children in sub-Saharan Africa have commenced antiretroviral therapy (ART). This thesis reviews the outcomes of published studies of paediatric ART cohorts in Africa, describes outcomes for children receiving ART in South Africa and examines determinants of mortality and generalizability across the Southern African region. Temporal trends in characteristics at ART initiation are also examined. The measurement of treatment success in resource-limited settings is reviewed, by examining virological failure, and assessing the diagnostic accuracy of immunological criteria for identifying virological failure.

The results chapter is presented in the form of published or submitted papers based on data from the International epidemiologic Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration. The first paper reviews paediatric ART studies from Africa published before 2008. Together with the literature review in chapter 1, it provides the background to this thesis. The second paper reports on mortality (8%) and retention in care (81%) by 3 years after ART start for >6,000 children who initiated ART in South Africa. The generalizable prognostic models in the third paper suggest that mortality during the first year on ART ranges from <2% to >45%, with the majority of children being in the group with the best prognosis. The fourth paper reports that 1 in 5 children meet criteria for confirmed virological failure by 3 years on ART. The risk is greater with triple ART containing nevirapine or unboosted ritonavir (in comparison with lopinavir/ritonavir or efavirenz). The fifth and sixth papers demonstrate that immunological criteria have low sensitivity and positive predictive value for virological failure. Targeted viral load measurement reduces the number of false positive virological failure diagnoses. The final paper shows that increasing numbers of children have initiated ART with a decline in disease severity at therapy start from 2005-

2010. However, even in 2010 a substantial number of children started ART with advanced disease.

The thesis concludes that access to ART for children has increased, with good outcomes. HIV cohort research is important in evaluating the safety and effectiveness of different models of care, treatment and monitoring strategies.

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- The University of Cape Town for a PhD completion grant that provided salary support to enable completion of this thesis.
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PREFACE

This thesis includes published papers, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town, and with the approval in 2011 of the University Doctoral Degrees Board. The following seven papers are formally included as part of the thesis:

1. Davies M, Egger M, Keiser O, Boulle A. Paediatric antiretroviral treatment programmes in sub-Saharan Africa: a review of published clinical studies. *African Journal of Aids Research* 2009; 8: 329-388.

2. Davies M, Keiser O, Technau K, Eley B, Rabie H, Van Cutsem G, Giddy J, Wood R, Boulle A, Egger M, Moultrie H for the International epidemiological Databases to Evaluate Aids Southern Africa (IeDEA-SA) collaboration. Outcomes of the South African National Antiretroviral Treatment (ART) Programme for children – The IeDEA Southern Africa Collaboration. *South African Medical Journal* 2009; 99: 730-737.

3. Davies M, May M, Bolton-Moore C, Chimbetete C, Eley B, Garone D, Giddy J, Moultrie H, Ndirangu J, Phiri S, Rabie H, Technau K, Wood R, Boulle A, Egger M, Keiser O. Prognosis of children with HIV-1 infection starting antiretroviral therapy in Southern Africa: a collaborative analysis of treatment programs. Submitted. 2013.

4. Davies M, Moultrie H, Eley B, Rabie H, Van Cutsem G, Giddy J, Wood R, Technau K Keiser O, Egger M, Boulle A. for the International epidemiological Databases to Evaluate Aids Southern Africa (IeDEA-SA) collaboration. Virologic failure and second-line antiretroviral therapy in South Africa – The IeDEA Southern Africa

Collaboration. *Journal of Acquired Immune Deficiency Syndromes* 2011; 56: 270-278

5. Davies M, Boulle A, Eley B, Moultrie H, Technau K, Rabie H, Van Cutsem G, Giddy J, Wood R, Egger M, Boulle A. for the International epidemiological Databases to Evaluate Aids Southern Africa (IeDEA-SA) collaboration. Accuracy of immunological criteria for identifying virological failure in children on antiretroviral therapy. *Tropic Medicine and International Health*. 2011; 16: 1367-71.

6. Davies MA, Boulle A, Technau K, Eley B, Moultrie H, Rabie H, Garone D, Giddy J, Wood R, Egger M, Keiser O. The role of targeted viral load testing in diagnosing virological failure in children on antiretroviral therapy with immunological failure. *Tropical Medicine and International Health.* 2012. epublished ahead of print.

7. Davies M, Phiri S, Wood R, Wellington M, Cox V, Bolton-Moore C, Moultrie H, Ndirangu J, Rabie H, Technau K, Giddy J, Maxwell N, Boulle A, Keiser O, Egger M, Eley B. Temporal trends in the characteristics of children at antiretroviral therapy initiation in Southern Africa: The International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Submitted. 2013.

The contribution of the candidate to each paper is outline in the introduction to each paper (pages 54, 66, 76, 117, 128, 139). The candidate was the lead and corresponding author for each paper, prepared all datasets for the analyses, conducted all the analyses and drafted all versions of the manuscripts. All co-authors critically reviewed and approved the submitted manuscripts, and the candidate was responsible for circulating the manuscripts to the co-authors, reviewing co-author comments and suggestions, and integrating them into the manuscript as appropriate. The supervisors of the candidate have separately confirmed to the

University of Cape Town Doctoral Degrees Board that the included papers overwhelmingly reflect the candidate's own scientific work.

The analyses are all based on data collected through the IeDEA Southern Africa (IeDEA-SA) Collaboration. The candidate has played a key role in the development and scientific leadership of IeDEA-SA, as the paediatric lead on the project from 2007-2010, and as joint principal investigator from 2011 onwards. As outlined in the section on data management (page 47), the candidate was instrumental in developing the IeDEA-SA data transfer protocol (DTP) and especially in adapting the DTP and data quality reports to be relevant for paediatric HIV cohort data collection and analysis. The candidate was involved in liaising with all collaborating paediatric sites regarding transfer of their data into the collaborative dataset. She was also personally responsible for extracting and developing analysis-ready datasets from the collaborative database for each of the analyses included in this thesis. The candidate has also been involved in primary data collection at Red Cross Children's Hopsital, one of the IeDEA-SA collaborating sites, both through establishing and overseeing the data collection system, and through ongoing involvement in provision of clinical care. Further details of the candidate's involvement in the specifics of data collection and management are included as part of the methods section of the introductory chapter (Chapter 1, Section 4, page 46).

LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AIDS	acquired imune deficiency syndrome
AMPATH	Academic Model for the Prevention and Treatment of HIV-AIDS
ARROW	AntiRetroviral Research for Watoto
ART	antiretroviral therapy
ART-LINC	antiretroviral therapy in low income countries
ARV	antiretroviral
AZT	zidovudine/azidothymidine
BAZ	body mass index-for-age z-score
BMI	body mass index
CDC	Centre for Disease Control
CER	comparative effectiveneness research
CHER	Children with HIV Early antiRetroviral therapy
CI	confidence interval
CY	child years
d4T	stavudine
DART	Development of AntiRetroviral Therapy in Africa
DBS	Dried Blood Spot
DHHS	Department of Health and Human Services
DRC	Democratic Republic of Congo
DTP	data transfer protocol
EFV	efavirenz
FDC	fixed dose combination
HAART	highly active antireroviral therapy

HAZ	height-for-age z-score
HICDEP	HIV Cohorts Data Exchange Protocol
HIV	human immunodeficiency virus
HR	hazard ratio
IeDEA	International epidemiologic Databases to Evaluate AIDS
IeDEA-SA	IeDEA Southen Africa
IF	immunological failure
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
ITT	intention to treat
KIDS-ART-LINC	paediatric antiretroviral therapy in lower income countries
LPV/r	lopinavir with ritonavir boosting
LR-	likelihood ratio of a negative test
LR+	likelihood ratio of a postive test
LTFU	loss to follow-up
MSF	Médecins Sans Frontières
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NPV	negative predictive value
NR	not reported
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OASIS	Observational Antiretroviral Studies in Southern Africa
OI	opportunistic infection
OR	odds ratio

PCR	polymerase chain reaction
PHC	primary health care
PhD	Doctor of Philosophy
PI	protease inhibitor
PMTCT	prevetion of mother to child transmission
PPV	positive predictive value
PREDICT	Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand
PY	person years
RCT	randomized controlled trial
ROC	receiver operating characteristic
RTV	ritonavir
sdNVP	single dose nervirapine
TAM	thymidine analogue mutation
TDF	tenofovir disoproxil fumarate
TFO	transfer out
TVL	targeted viral load
UCT	University of Cape Town
VF	virological failure
VL	viral load
WAZ	weight-for-age z-score
WFHZ	weight-for-height z-score
WHO	World Health Organization

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Figures not included in published papers

Tables not included in published papers

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

In 2009 when this study was conceived, Sub-Saharan Africa was home to an estimated 2.3 million children under the age of 15 years living with HIV, with 330,000 in South Africa alone.[1,2] Although access to antiretroviral therapy (ART) for these children was initially slow and lagged far behind access for adults, this had expanded rapidly in recent years, but continued to reach only a fraction of those in need.[2,3] For example, across sub-Saharan Africa the percentage of children in need of ART that were receiving it increased from 6% in 2005 to 26% in 2009.[2] In South Africa, paediatric ART access had expanded particularly rapidly – by December 2009 an estimated 54% of the 160,000 children in need of ART were receiving it. Nevertheless many challenges to scaling up paediatric ART remained including poor access to early infant diagnosis, limited availability of suitable drug formulations, lack of integration of antenatal and maternal and child health programmes with HIV care programmes, and the complexity of providing HIV care and treatment for very sick young infants and children resulting in care largely centralized at urban or specialist facilities.[4-6]

Since 2004, an increasing number of publications from individual treatment programmes in sub-Saharan Africa had demonstrated both the feasibility and effectiveness of paediatric ART in this setting.[7-17] In addition, in 2009, the combined paediatric antiretroviral therapy in lower income countries (KIDS-ART-LINC) cohort collaboration demonstrated that in 2,405 children followed for a median of 20 months, the 2-year risk of death after ART initiation was 6.9%, while the risk of loss to follow-up was substantially higher at 10.3%.[18]

As access to paediatric ART was expanding with children remaining on therapy for longer durations, there was a need to describe longer term outcomes on ART and their individual

and programme-level determinants in large cohorts of children treated in a range of different countries and programmes. Such analyses could inform clinical practice and programmatic roll-out of ART. In particular, analyses were needed that described ART effectiveness and monitoring strategies in the context of the challenges to paediatric ART scale-up. This was particularly important in the light of paediatric ART guidelines that had evolved substantially since 2004 in accordance with scientific evidence.[19-22]

The International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) was initiated in 2006 and is one of seven IeDEA regional collaborations across the world (http://www.iedea-hiv.org).[23] The IeDEA-SA paediatric cohort collaboration aims to collect and harmonize paediatric HIV data across the Southern African region to address research questions unanswerable within a single cohort.[24] The IeDEA-SA paediatric combined cohort therefore provided a unique opportunity to examine ART outcomes and effectiveness in large cohorts of children from different programmes and settings across the Southern African region. This study therefore aimed to report on the outcomes and their determinants for children initiating ART both within the South African national programme and across the Southern African region.

1.2. Aims and objectives

The aim of this study was to describe the effectiveness and determinants of effectiveness of paediatric ART programmes across Southern Africa at the time the study was developed in 2009.

Specific objectives were:

1. To review the literature on paediatric ART effectiveness and outcomes in sub-Saharan Africa.
2. To describe the survival and related outcomes of ART programmes in Southern Africa and their determinants through two analyses as follows:
    a. To describe the survival and related outcomes of the South African ART programme for children, and examine determinants of these outcomes.
    b. To assess the generalizability of survival outcomes on ART across the Southern African region by developing a prognostic model of one–year mortality for children initiating ART that is generalizable across different treatment cohorts.
3. To evaluate the role of different monitoring strategies for measuring treatment success in children retained in care in resource-limited settings, and examine the determinants of virological failure through three analyses as follows:
    a. To analyse the probability and determinants of virological failure and switching to second-line therapy in the South African ART programme.
    b. To examine the diagnostic value of immunological criteria for identifying virological failure in children on ART.

c. To examine the role of targeted viral load strategies contingent on meeting immunologic failure criteria for identifying patients with virological failure, in the context of limited access to HIV-RNA measurement.

4. To examine programmatic ART scale-up through describing the characteristics of children accessing ART across Southern Africa and examining temporal changes in these characteristics from 2004 – 2010 in relation to changes in WHO and national paediatric HIV treatment guidelines.

1.3 Literature review

1.3.1 Introduction

As early as 1999, studies demonstrating good outcomes of paediatric triple ART were published from resource rich settings.[25-30] Since 2004, access to ART in resource-limited settings, and Africa in particular, has increased dramatically.[1,31,32] This has been both due to increasing country and programme capacity to enrol children on ART with substantial external donor support, and guideline changes advocating earlier ART at higher CD4 thresholds.[20,22,32] These changes have been based on the rapid disease progression in the absence of ART, as well as the mortality benefit of ART in infants.[33-35] Nevertheless, ART continues to reach only a fraction of those who need it; by the end of 2011, 42 countries provided ART to fewer than one in five treatment-eligible children.[32]

There are a number of barriers to providing ART for children in resource-limited settings including poor access to early infant diagnosis, few and expensive drugs available in child-friendly formulations, need for a reliable caregiver to administer medication, and both the real and perceived complexity and lack of expertise and experience with treating and monitoring sick infants and young children.[4,5,36,37] It is therefore important to review the characteristics of children currently accessing ART in resource-limited settings, their outcomes on therapy and the determinants of these outcomes. This includes reviewing and evaluating the different monitoring strategies used to measure these outcomes.

1.3.2 Aim

This literature review aims to appraise all published observational studies of ART for HIV-infected children in sub-Saharan Africa in routine clinic settings that report on mortality outcomes from an entire cohort of children initiating therapy. For the purpose of this thesis,

ART will be defined as a regimen of at least three drugs from two different classes. The review will include studies published in English until the end of 2010 in order to provide a context for the analyses included in this thesis at the time when they were conceptualized. A published literature review of all studies published until the end of 2007 is included as one of the published papers in this thesis (Chapter2, section 2.1 page 53). This section of the thesis will therefore focus on studies published between 2008 and 2010 as studies prior to 2008 are described and appraised in detail in the published review. In addition, studies published between 2008 and 2010 provide the most relevant background to this thesis, as this is the period during which it was conceptualized.

The objectives of the review are to report the following items as well as identify needs for further research:

- Characteristics of children at ART initiation and how these have changed over time and in different settings.
- Response to ART including mortality and loss to follow-up, growth, opportunistic infections, immunological and virological response.
- Determinants of response to ART.
- Virological failure and the role of clinical and immunological responses to ART in identifying children with virological failure in the absence of routine HIV-RNA monitoring.

While the key studies to be *systematically* reviewed will therefore be studies of sub-Saharan African paediatric ART outcomes that report on mortality, I will also selectively draw upon other studies that include results pertinent to these objectives. These include studies from resource-limited settings outside sub-Saharan Africa (e.g. Jittamala *et al.*, 2009[38]), studies that report on clinical responses other than mortality, often only in selected children surviving

beyond a certain initial period after ART initiation (e.g. Kabue *et al.*, 2008[39]), results from dedicated research studies rather than routine clinic settings (e.g. Musoke *et al.*, 2009[40]; Reitz *et al.*, 2010[41]), reports of ART monitoring strategies (e.g. Yotebieng *et al.*, 2010[42]) and resistance (e.g. Adje-Toure *et al.*, 2008[43]) and comparisons of ART outcomes between resource-limited and wealthy countries (e.g. Kekitiinwa *et al.*, 2009[44]).

1.3.3 Search strategy

A search of the Medline bibliographic database using the PubMed interface (National Library of Medicine, Bethesda, MD) was performed using the following strategy: "(antiretroviral OR ART OR HAART OR cART") AND (child* OR pediatric OR paediatric) AND Africa". A key word search was used as this yielded more studies than that of Medical Subject Headings. In addition, the bibliographies of reviews of paediatric ART outcomes in resource-limited settings (identified through PubMed) were reviewed to identify additional studies.

Inclusion criteria:

- Articles from sub-Saharan Africa that reported at least on the mortality outcomes of entire cohorts of children that initiated ART in a routine clinic setting were included.
- Published in English.

Exclusion criteria

- studies from countries not in sub-Saharan Africa.
- studies that did not report on mortality.
- studies that reported outcomes on only a subset of all children that initiated treatment.
- studies from non-routine care settings (e.g. trials and dedicated observational cohort studies with inclusion criteria that could constitute a selection bias).
- studies where most children were treated with <3 antiretrovirals (ARV).

Possible duplicate studies were included as it was difficult to confidently ascertain whether the data included was the same, and repeat studies on the same cohort frequently demonstrated evolution of the programme and provided additional data such as increased cohort size, longer follow-up and more detailed information on particular outcomes. Similarly collaborative studies and reports of programme level data that may include data from cohorts that have also published individual cohort results were all included, so data from some individual cohorts might be included more than once. It is important to include the collaborative studies as they provide valuable background to this thesis which is based on a collaborative dataset. Collaborative studies frequently include a broader spectrum of HIV care settings as programmes that are not able to undertake independent research can be included. In contrast, individual patient studies can frequently describe programmes to a greater level of detail with better data completeness. Published abstracts were reviewed to determine whether studies met the inclusion criteria, and the full text of articles was reviewed if this was not clear from the published abstract.

1.3.4 Results

Numbers of studies included

Forty-one studies were identified that met the inclusion criteria; 18 of these were published prior to 2008 and are included in the published literature review; 23 studies published between 2008 and 2010 are reviewed in the following section.

Characteristics of included studies

The characteristics of 23 studies (2008-2010) systematically reviewed are shown in Table 1. (Table 1 of the published review describes studies published prior to 2008). Two of the 23 studies report outcomes based on aggregate data from the Western Cape Provincial ARV

programme in South Africa and appear to report on a largely similar paediatric dataset. [45,46] The 21 studies that analyse individual patient data report on 20 different cohorts or cohort collaborations, with two studies reporting on similar data from three facilities in Zambia. [47,48] Four are repeat studies in cohorts that were included in the published literature review, namely the *Médecins sans Frontières* (MSF) cohort collaboration,[16,17,49] Kenyatta National Hospital, Nairobi,[50,51] Academic Model for the Prevention and Treatment of HIV-AIDS (AMPATH), Kenya,[52,53] and Lusaka, Zambia.[12,54] In addition to the MSF cohort collaboration,[49] the KIDS ART-LINC collaboration reports on several HIV programmes from a number of countries across Africa.[18] Ten reported studies include data from more than one clinic within one country[47,48,53-61] and eight studies are from a single clinic/health facility.[51,62-68] Eight studies are from primary health care (PHC) clinics, five from hospital-based clinics, seven include both PHC and hospital data, and one is from a hospice setting in which a multidisciplinary team provides daily care to children with very advanced disease.[65] In addition to the two studies reporting provincial programme data, six studies were from South Africa, three from Kenya and two each from Zambia and Uganda. There was one study each from Rwanda, Democratic Republic of Congo (DRC), Côte d'Ivoire, Mali and Malawi. Eligibility criteria for ART initiation were mostly based on World Health Organization (WHO) guideline criteria in place at the time. This means that for some studies ART initiation criteria changed during the study with revisions in WHO guidelines and that CD4 thresholds used for ART initiation are lower than those currently recommended in the WHO 2010 guidelines.[22] In addition, in some studies HIV DNA or RNA polymerase chain reaction (PCR) testing was specifically stated to be unavailable for some or all of the study period.[47,48,64,69]

Time of data collection

Data collection for the majority of studies began in 2004 and mostly corresponds to the start of national ARV programmes. Data collection ended between 2006 and 2008, so studies do not include significant numbers of infants started prior to disease progression as recommended by the interim WHO report in 2008.[21]

Numbers and sex of children initiated on ART

As expected, multi-country collaborative studies included large numbers of children. The MSF collaborative study included 3,542 children from Africa[49] while the KIDS-ART-LINC collaboration included nearly 2,500 children.[18] The number and size of single country collaborative studies is increasing. For example, the AMPATH collaboration in 2009 reported on >2,500 children on ART,[53] nearly tenfold more than in 2006.[52] In South Africa, Fatti *et al.*[59] include 2,332 children ever started on ART, while the Western Cape Provincial programme report includes approximately 1,700 children.[45,46] Including all studies, 21,524 children who ever initiated ART are included, of whom nearly 6,000 are from the two multi-country collaborative studies. Among studies that include more than one cohort from a single country the median (interquartile range [IQR]) number of children included is 770 (542-1,754). Single cohort studies continue to include relatively small numbers of children with median (IQR) of 149 (84-345). In contrast, prior to 2008 the largest MSF multi-country study included 1,184 children, the median (IQR) number of children in multisite studies from one country was 279 (233-297) and from single cohort studies was 80 (73-244). In general boys and girls are equally represented.

Table 1: Characteristics of included studies of paediatric ART outcomes in Africa and child characteristics at ART start published from 2008-2010

Study	Country	No. of sites	Observation time	No. of children on ART	Percentage females	Median (IQR) age (years)	Median (IQR) CD4%	Percentage CD4 <15%	Percentage advanced stage	Median (IQR) WAZ	Proportion WAZ <-3	Median (IQR) log_{10} viral load
KIDS-ART-LINC Collaboration 2008	countries in West, East and Southern Africa	16	until 2007	2,405	48	4.9 (2.1-8.4)	NR	73[d]	53[e]	NR	35	NR
Barth *et al.* 2008	South Africa	1	2003-2006	66	50	4.8 (2.6)[a]	10.6 (0.1-29.8)[b]	NR	NR	NR	NR	5.1 (3.0-5.7)[b]
Jaspan *et al.* 2008	South Africa	1	2002-2006	391	47	2.2 (1.0-4.5)	13.0 (8.0-17.5)	NR	NR	-2.5 (-4.0 to -1.2)	NR	5.5 (4.8-6.0)
Kiboneka *et al.* 2008	Uganda	10	2004-2008	770	54	9 (5.0-13.0)	NR	47	42	NR	NR	NR
Van Griensven *et al.* 2008	Rwanda	2	2003- 2006	315	50	7.2 (4.5-10.4)	14.0 (9.0-18.0)	56	40	-1.9 (-3.0 to -0.9)	NR	NR
Van Winghem *et al.* 2008	Kenya	4	2003-2007	657	50	5.5 (3.2-8.7)	NR	NR	NR	NR	NR	NR

Study	Country	No. of sites	Observation time	No. of children on ART	Percentage females	Median (IQR) age (years)	Median (IQR) CD4%	Percentage CD4 <15%	Percentage advanced stage[a]	Median (IQR) WAZ	Proportion WAZ <-3	Median (IQR) log_{10} viral load
Bock *et al.* 2009	South Africa	many	2004-2006	1,741	NR	NR	NR	46	NR	NR	NR	NR
Boulle *et al.* 2009	South Africa	many	2002-2006	1,709	NR	NR	NR	45	NR	NR	NR	NR
Callens *et al.* 2009	DRC; Pediatric Hospital	1	2004-2006	299	48	NR	12.0 (7.0-18.0)	NR	76	NR	30	NR
Harding *et al.* 2009	South Africa, hospice	1	2006	37	54	5.5 (3.3)[a]	13.6[a] (8.6)[c]	NR	NR	NR	NR	5.4 (5.0-5.9)
Mubiana *et al.* 2009	Zambia	13	2004-2006	1,235	45	6.4 (2.4-9.9)	12.6[a] (8.2)[c]	NR	76	-2.3[a] (1.7)[c]	34	NR
Ntanda *et al.* 2009	Uganda	1	2002-2008	101	56	6 (3-10)	non-orphans: 9.0 (5.0-11.3) orphans: 9.0 (5.9-10.2)	NR	non-orphans: 17 orphans: 36	NR	NR	NR
Nyandiko *et al.* 2009	Kenya	18	2002-2008	2,576	NR	4.5 (0-14.2)[b]	13.0 (0-62.0)[b]	NR	44	NR	NR	NR

Study	Country	No. of sites	Observation time	No. of children on ART	Percentage females	Median (IQR) age (years)	Median (IQR) CD4%	Percentage CD4 <15%	Percentage advanced stage[a]	Median (IQR) WAZ	Proportion WAZ <-3	Median (IQR) log_{10} viral load
Anaky *et al.* 2010	Cote d'Ivoire	19	2004-2007	977	47	5.3 (2.3-9.1)	10.7 (5.6-15.0)	NR	43	-3.0 (-4.7 to -1.8)	NR	NR
Fatti *et al.* 2010	South Africa	51	2003-2008	2,332	50	5.8 (3.0- 9.0)	12.2 (7.0-18.0)	73[d]	67	-1.51[a] (-1.59 to -1.44)[g]	15	NR
Germenaud *et al.* 2010	Mali	1	2006-2007	97	46	2.6 (1.7-5.8)	NR	NR	77	-3.0 (-4.7 to -2.2)	NR	NR
Janssen *et al.* 2010	South Africa	many	2004-2008	477	48	6.2 (0.3-15.0)[b]	17.0 (11.0-26.0)	NR	67	-1.8 (-2.5 to -0.8)	NR	4.2 (3.2-5.2)
Naidoo *et al.* 2010	South Africa	2	2004-2005	120	46	6.5[a] (1.7-12.5)	9.3[a] (5.4)[c]	NR	NR	-1.96[a] (1.78)[c]	23	4.8[a] (1.1)[c]
Sauvageot *et al.* 2010	15 countries in Africa, 5 in Asia	48	2002-2008	3,936	47	2.6 (1.7-3.7)	NR	82	76	-2.3 (-3.3 to -1.2)	31	NR
Sutcliffe *et al.* 2010a	Zambia	3	2004-2008	607	NR	urban 7.1 (3.6-10.2) rural 8.1 (3.4-10.1)	NR	NR	NR	NR	NR	NR
Sutcliffe *et al.* 2010b	Zambia	3	2004-2008	863	NR	urban 6.8 (3.2-10.0) rural 3.7 (1.9-8.3)	urban 11.1 (6.5-16.2) rural 14.3 (9.8-19.0)	NR	NR	urban -2.3 (-3.5 to -1.4) rural -3.1 (-4.1 to 1.8)	NR	NR
Wamalwa *et al.* 2010	Kenya	1	2004-2008	149	50	4.9 (2.6-6.7)	6.8 (3.6-11.4)	89	14[f]	-2.35 (-3.14 to -1.49)	NR	6.0 (5.4-6.5)
Weigel *et al.* 2010	Malawi	1	2001-2008	497	49	8.0 (4.0-11.0)	10.8 (7.2-15.7)	77	94	-2.1 (-2.7 to -1.3)	NR	NR

NR Not reported; IQR interquartile range

[a]mean; [b]range; [c]standard deviation; [d]severe immunodeficiency; [e]severe clinical status (WAZ<-3 or WHO Stage III/IV); [f]Stage IV; [g]95% Confidence Interval

Missing data on characteristics at ART initiation

While multi-site studies include large numbers of children, this may be at the expense of data quality and completeness. This is particularly a problem for multi-country studies and studies that include numerous sites within a country. For example, the KIDS-ART-LINC collaboration used a composite variable called 'severe clinical status' that combined WHO Clinical Stage and weight-for-age z-score (WAZ) data due to substantial missing data on both of these variables individually. Both WHO Clinical Stage and WAZ data were missing for nearly 40% of children.[18] In the MSF collaborative dataset, CD4% data was only available for 60% of children.[49] Similar proportions of missing CD4% data were noted in the study of >2,000 children from 44 public health facilities across South Africa.[59] The reasons for missing data are complex and may be different for different studies. Variables may not actually be measured due to lack of equipment or technology (e.g. anthropometric variables, CD4, HIV-RNA), lack of expertise (e.g. lack of knowledge of WHO Staging), treatment guidelines not requiring their measurement (e.g. baseline CD4 and HIV-RNA measures are not routinely done in many resource-limited settings) or health care workers in busy clinics omitting to perform every measurement in every child. Availability of clinical and laboratory data according to national monitoring guidelines may be a proxy for quality of care [45,46] and Fatti *et al.*[59] noted that missing laboratory result data was higher at rural facilities. Even where variables are measured, measurements may not be recorded in medical records and/or transferred to electronic databases used for analysis. As ART programmes expand and children are on therapy for longer durations, there is likely to be increased transfer of children between treatment sites, and records of treatment characteristics at ART start may not be available at the new treatment site. Fatti *et al.*[59], for example, excluded 17% of children who started treatment at another site from their analysis. Missing data may also arise when data

collection is done by retrospective record review and there is selective access to medical records as was reported by two studies.[54,61]

Characteristics at ART initiation

Age

The age at which children initiate treatment in routine care settings is a measure of the extent to which infants and young children are being timeously diagnosed and started on ART. In the absence of treatment, HIV disease progression and mortality is greatest in infants and young children,[34,35,70-72] and ART initiation before clinical progression in young infants reduces mortality by 75%.[33] In addition, in a cohort of children aged 1-10 years ineligible for ART according to WHO 2006 criteria, 19% progressed within two years to death, a WHO Stage III/IV event, or to meet WHO 2006 CD4 thresholds for ART initiation. Children with low CD4%, high HIV-RNA and age <3 years had the greatest risk of progression. For example, a child with HIV-RNA $>10^5$ copies/ml and CD4% <25 had progression probability of nearly 30% in one year.[73]

Children in the studies reviewed continue to initiate ART at older ages with mean/median ranging from 4.8-9.0 years in all except three studies. One of these studies specifically only included children less than five years of age[49] while the others are both from tertiary care hospital settings with median (IQR) ages at ART start of 2.6 and 2.2 years respectively.[63,67] Age ranges reported may however be misleading as they are dependent on the inclusion criteria for the particular cohort – for example some cohorts specifically exclude children less than 18 months[51] while the upper limit for inclusion ranged from 12 to 18 years.

Access to early infant diagnosis and coverage of routine infant testing is critical for accurately identifying infected children. In this respect some studies reported that diagnosis in children <18 months of age was presumptive for part or all of the study.[47,48,54] A study of

health facilities in Kenya published in 2008 showed that while a policy framework for identifying HIV- infected children had been established, there were a number of barriers to systematic diagnosis including limited postnatal follow-up of exposed children and access to HIV PCR testing at only four of 58 health facilities providing paediatric ART.[74] While clinical algorithms have been proposed to aid diagnosis in infants in the absence of PCR testing, these lack sensitivity and specificity, although may be useful for identifying those at greatest risk of progression or for excluding the diagnosis.[75,76] Where access to Dried Blood Spot (DBS) polymerase chain reaction (PCR) testing is available, it has been shown to be feasibly and successfully integrated into public health programmes, by, for example, implementing routine testing at immunization visits.[77,78] Even where PCR testing is available, attrition from prevention of mother to child transmission (PMTCT) programmes between birth and the six week infant diagnosis visit is frequently high[79,80] and so routine provider initiated testing either on hospital admission or at other health visits can increase both coverage of infant diagnosis and numbers of children initiating ART.[78,81]

Interestingly the only study reviewed that assessed secular trends in age of children initiating ART found no change over time in an urban programme but a reduction in median age from 8.1 to 3.1 years in the rural programme which included follow-up of HIV exposed uninfected infants suggesting that integrated PMTCT follow-up and ART services may be better at identifying and initiating infants and young children on ART.[47] Even in this setting, the majority of children already had advanced disease by the time of ART start with median (IQR) CD4% of 13.7 (9.5 – 18.4) and 67% of children with WAZ<-2.

The fact that the only cohorts with median age <36 months were tertiary care hospital settings[63,67] suggests that even with good access to early infant diagnostic testing, there are many additional barriers to care.[4-6] The same pattern was seen in studies prior to 2008 with a median age of 1.9 years for the Red Cross Children's Hospital tertiary care cohort that was

markedly younger than any of the other studies.[10] These barriers include the need for syrup formulations of medication with regular dose adjustments due to rapid infant growth. The MSF Collaboration[49] reported the need to use different drugs in younger children (zidovudine [AZT] instead of stavudine [d4T]) for formulation-related reasons and in the Rwandan study (median age 7.2 years) syrups were only available for the later part of the study period prior to which younger children had to be referred to the central hospital.[56] A study of ART outcomes in HIV-infected Ugandan children with and without exposure to single dose nevirapine (sdNVP) initially only included children >12 months using fixed dose combination (FDC) drugs.[40] However the study protocol had to be amended to include children 6-12 months of age using syrup formulations in order to recruit sufficient numbers of children with sdNVP exposure, most of whom were infants.[40]

A further barrier to infant ART at primary care level is the reality of high risk of disease progression and mortality in young infants, especially those infected *in utero* or perinatally, even when ART is started early.[82,83] Hospital referral may be required and PHC staff may be understandably reluctant to initiate treatment without tertiary care support. Even in the trial setting of the Children with HIV Early antiretroviral (CHER) Study conducted at tertiary hospitals, overall mortality in the early therapy group was still high at 4.9/100 person-years (PY) for the full follow-up period, and extremely high at 9.8% during the first 12 weeks after ART initiation.[33]

Clinical Stage

The majority of children started ART with advanced (WHO Stage III/IV) clinical disease across all studies that reported it. The MSF cohort collaboration[49] reported 76% of children with known Stage having Stage III/IV disease (Stage not reported in 11% of children) and in the KIDS-ART-LINC collaboration 53% of children had either Stage III/IV Disease or

WAZ<-3 (although information on both of these was missing for nearly 40% of children).[18] Seven of the ten single country multi-site cohorts reported on WHO Clinical Stage. Missing Stage data was minimal for four of these studies and 4%, 13% and 21% in the remaining three studies. Five of the single clinic studies provided information on WHO Stage with missing data of 20% in only one study.[68] While many studies report high proportions (>65%) of children having Stage III/IV disease, and up to 94% in the Malawi cohort,[68] four studies had lower proportions (40-50%) of children with advanced disease.[53,55,56,58] The proportion of children with advanced disease seems higher in the pre-2008 studies where almost all studies had >70% and three cohorts >85% of children with Stage III/IV disease.[10,15,84]

Nutritional status

Weight-for-age z-scores (WAZ) were reported as medians/means for 11 studies and percent of children less than <-2 (two studies) or -3 (six studies). For most studies median WAZ was between -3 and -2.3, apart from three studies with median/mean WAZ >-2, all of which are from primary care cohorts within South Africa, possibly reflecting less severe disease in children treated at primary care level in South Africa.[59,61,85] Similarly >30% of children had WAZ<-3 in all but two studies, both of which are mentioned above.[59,61] Missing weight data was substantial and reported by six studies, ranging from 5% to 51%. This is a concern as weight measurement is required to determine ARV dose. However, missing weight data does not necessarily mean that the measurement was not done or known by the attending clinician, and may reflect the discrepancy between recording of electronic data and what is actually measured in the clinic. These findings are very similar to those reported for cohort results published prior to 2008.

Height-for-age z-scores (HAZ) were reported by only five studies and were consistently lower than WAZ except in the small Mali study,[67], with values ranging from -2.6 to -2.3.

Callens *et al.*[64] reported 27% of children with HAZ<-3 and Weigel *et al.*[68] 69% with HAZ <-2. Median weight-for-height z-score (WFHZ) was only reported for two studies at -0.45[61] and -1.13[51] respectively. The paucity of studies reporting on height and weight-for-height data suggest that this is not routinely recorded and even in those studies with this information, two reported missing data in approximately one quarter of children. Weight and height measurement, together with assessment of oedema is needed to classify nutritional status, so the anthropometric measures reported by these studies do not provide a comprehensive assessment of nutritional status of children initiating ART. WHO recommends dosing using weight bands except in children less than three years of age, and the lack of height measurement suggests that dosing is indeed largely weight-based.[20]

In a comparison of children initiating therapy in Uganda with a collaborative cohort in the UK/Ireland, the median WAZ and HAZ in Uganda were significantly lower than in the UK (-2.8 vs -0.6 and -2.8 vs -0.8) respectively.[39,44] Similarly, in a comparison of paediatric ART outcomes between resource-limited and developed countries, mean baseline WAZ was -2.2 for resource-limited setting and -0.4 for developed countries.[27]

Immunological status

Eighteen studies reported some measure of immunological status (median/mean CD4 count or percent or proportion with values below thresholds defining immune suppression). As with other variables the proportion of missing data was substantial with 11 studies reporting >5% missing data and the proportion missing ranged from 8-40%. In most studies mean/median CD4% at ART start was low (range 9.3 to 14.0 for most studies.) This is, however, higher than for studies published pre-2008 in which the median CD4% was below 10% in all but two studies, both of which included relatively larger numbers of young children. In comparison, the mean CD4% of children starting ART in developed countries has been

reported as 23% [27].

One study reported a much lower median CD4% of 6.8, but this study only enrolled children with WHO Stage III/IV or CD4<15% and was based at the Kenyatta National Hospital in Nairobi, so perhaps likely to see children with the most severe disease.[51] In contrast, in rural KwaZulu-Natal the highest median CD4% of 17% was reported in a relatively old cohort of children (median age 6.2 years) however there was substantial missing data so there may be selection bias.[60]

Median CD4 count was variable in keeping with the different age ranges of children, but for most studies was between 250 and 500 cells/mm^3. Notable exceptions of lower median CD4 were reported in the subset of children >13 years of age in DRC,[64] and among orphans with median age of seven years in Kenya.[66] In the Cape Town cohort with median age of 26 months, the median CD4 at ART start was higher at 513 cells/mm^3.[63] There has not been widespread adoption of the use of CD4 z-scores[86] which would make it easier to compare CD4 values across different age ranges, perhaps because of the variability of normal values across populations and lack of reference values for different populations, and the fact that CD4% values are relatively comparable except in infants and very young children.

Viral load

As expected, few studies provided information on HIV-RNA as this is frequently either not available or not measured at ART start in resource-limited settings. Most of the studies that did report HIV-RNA information were single site cohorts, suggesting again that this information is not routinely available across a range of settings. Missing data was >50% in three of these cohorts, all of which are South African, where national guidelines actually recommend measurement of HIV-RNA in children prior to treatment initiation.[60,61,63]

Clinicians may have been influenced by adult guidelines that do not recommend measurement of baseline HIV-RNA, especially in sites where both adults and children are treated in the same clinic. In four of the six studies with baseline HIV-RNA measurements, the median (IQR) HIV-RNA was >5 $\log_{10}$ copies/ml; the two studies with lower values were both cohorts of older children (median age >6 years), in keeping with the known decline of HIV-RNA with increasing age.[87] In particular, the study at rural PHC clinics in Kwazulu-Natal with the lowest median HIV-RNA value of 4.2 $\log_{10}$ copies/ml also had the highest median CD4% value of 17% despite being a relatively older cohort with median age of 6.2 years and only 12% of children <18 months of age.[60] This suggests that this is a selected population of healthier children, with sicker children possibly starting treatment in urban areas or at the local district hospital.[60] Prior to 2008, median HIV-RNA values were >5 $\log_{10}$ copies/ml in all studies that reported it. In comparison, the mean baseline HIV-RNA in studies from developed countries is 4.7 $\log_{10}$ copies/ml.[27]

Caregivers and orphan status

Six studies provided information on the child's caregiver and/or proportion of children for whom parents were deceased. It is difficult to compare the proportion of orphaned children across studies as the definition of orphanhood is different and the proportion of children who have been orphaned is expected to be higher in studies that include mostly older children. The proportion of children reported to be orphans ranged from 25% to 47%, however it is likely that studies with higher estimates define children who have lost one parent to be orphans although this is not always specifically stated.[64,66] Two studies report on the proportion of children with both parents deceased as 7% [51] and 11% [53] respectively. There is also substantial missing data on orphan status (up to 30% reported by two studies).

Orphans are older at ART start and may have more advanced disease in terms of Clinical Stage,[66] immune suppression[55] and WAZ[53], although this is not consistent across studies. Using the same cohort in Western Kenya, Nyandiko *et al*.[52] were the only researchers prior to 2008 to compare characteristics by orphan status at ART initiation and found no significant differences except for older age in orphans, but did not specifically report on WAZ in that study. It has been argued that orphanhood predicts delayed access to ART.[66] There is however a selection bias among older children as children are both more likely to become orphaned and more likely to have advanced disease as they grow older (as both their and their parents' disease has had a longer time to progress). It would be more accurate to say that older children initiating ART are more likely to be orphans and have advanced disease, than to infer delayed access for orphans. The fact that almost all studies have found no differences in adherence or outcomes on ART between orphans and non-orphans suggests that orphan status does not affect quality of care on ART, and so may well not be associated with worse access to ART.[52,53,66,88-91]. The only exception is the finding of poorer adherence for double orphans in a study by Vreeman *et al*.[92] There is however a selection bias when examining outcomes on ART as orphans with more diligent caregivers are those most likely to access treatment.

Tuberculosis

Eight studies report on tuberculosis at ART initiation with proportions in all except one study ranging from 2.5%-8%, which is similar to proportions reported from most studies prior to 2008. A much higher proportion of 22% is reported from a cohort in rural Kwazulu-Natal in South Africa.[60] While it is unclear whether the proportion in the Kwazulu-Natal cohort includes both children with active tuberculosis and previous tuberculosis, similar high proportions of children with tuberculosis were reported from two studies prior to 2008,[11,93]

and also from more detailed cohort studies of tuberculosis in HIV-infected children that did not meet inclusion criteria for this review.[41,42,94] For example, Martinson *et al.*[94] found that 21% of children had a tuberculosis diagnosis either at enrolment into their study, or within the next few weeks. Alarmingly, in a cohort analysis of data prior to randomization on the NEVEREST trial of different treatment strategies in children initiating protease inhibitor (PI) -based ART, 24% of children aged less than two years of age were on tuberculosis treatment at ART start.[41] Nearly 40% were co-treated for tuberculosis at some point during follow-up.[41] While such high proportions of children with tuberculosis may not be surprising in view of the estimated incidence of 23.4 cases per 100 HIV-infected children per year,[95] they are concerning as treatment of children co-infected with tuberculosis may lead to increased medication burden with the risk of poor adherence, greater chance of drug-drug interactions and the need to modify regimens in children taking lopinavir/ritonavir (LPV/r)-based or nevirapine (NVP)-based regimens.[22,96,97] There is also a risk of developing paradoxical worsening of tuberculosis on treatment due to the immune reconstitution inflammatory syndrome (IRIS). [98,99] Indeed, although most studies have not demonstrated survival differences between children co-treated for tuberculosis and those receiving ART alone,[41,100] tuberculosis is a significant cause of mortality in HIV-infected children with 18-44% of deaths attributable to tuberculosis in studies from tuberculosis endemic areas.[51,101] Further, a lower probability of viral suppression in children on ART co-treated for tuberculosis has been reported.[41]

Nevertheless, it is widely acknowledged that comparisons of proportions of children with tuberculosis in different studies is difficult as the proportion diagnosed with tuberculosis may depend on the extent of active screening for tuberculosis prior to ART initiation, access to diagnostic facilities and diagnostic algorithms or scoring systems used,[102-104] degree of

integration of tuberculosis and HIV programmes and the relative importance of tuberculosis programmes as a referral sources to HIV/ART care. Indeed, in many studies classification of children as having tuberculosis is based on treatment for tuberculosis rather than confirmed diagnosis,[41,94,105] precisely because of the diagnostic difficulties in young children. In the face of diagnostic uncertainty, there may well be over-treatment for tuberculosis to avoid missed opportunities to treat a potentially curable opportunistic infection. The proportion of children reported as having previous tuberculosis either at enrolment into HIV care or at ART start is high, ranging from 18- 42% [49,53,64,105] in all except one study from Côte d'Ivoire. [58]

Other illnesses at ART start

As expected with most children having advanced clinical disease, the proportion of children with opportunistic infections (OI) prior to ART initiation is high in the four studies that report it. Callens *et al*.[64] found that 76% of children had at least one OI diagnosis prior to ART start, and a similar proportion of children with at least one previous hospitalisation has been reported.[51] A slightly lower proportion with severe disease is reported at enrolment into care when not all children have met ART eligibility criteria.[53] Common diagnoses/symptoms include oral candida, respiratory illnesses, mucocutaneous conditions, gastroenteritis, failure to thrive and delayed milestones. Similar OIs are reported in studies of hospitalisation of HIV-infected children (both off and on ART),[101] with the addition of malaria as a common diagnosis in a study from Ghana.[106] In a cohort of children referred for palliative hospice care, diagnoses reflected the effects of chronic HIV infection such as encephalopathy, tuberculosis, lymphoid interstitial pneumonitis and cor pulmonale.[65]

First-line drug regimens

Most studies report either on the recommended first-line regimens according to programme or country guidelines or provide information on drugs actually prescribed. The majority of children across studies were initiated on a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) + one non-nucleoside reverse transcriptase inhibitor (NNRTI) with NVP dominating as the NNRTI of choice in most studies. This is both in keeping with WHO guidelines[20] and reflects the availability of fixed dose combinations (FDC) including NVP that were specifically reported to be used where possible in four studies.[49,54,56,68] These studies noted increased complexity of prescribing for younger children for whom syrup formulations were needed. Similar patterns of regimen use were noted in studies prior to 2008, with a number of studies reporting use of split adult FDC tablets in children, even in children < 8kg.[15,16,100,107] This meant once-daily dosing of d4T which is not recommended, but nevertheless had good outcomes and was simple, available and low cost.[15]

PI use was only reported in three studies, two of which were from South Africa with proportions of 25% in predominantly primary care settings[59] and 52% in a younger cohort treated at a tertiary hospital.[63] One-third of children in the Côte d'Ivoire cohort started a PI-based regimen.[58] LPV/r was used in South Africa and nelfinavir in Côte d'Ivoire. In the KIDS-ART-LINC collaboration that includes cohorts both from West Africa and South Africa, 41% of children initiated PI-based regimens.[18] As expected, PI use was more common in younger children due to lack of dosing recommendations for efavirenz (EFV) in children less than three years of age and higher likelihood of exposure to antiretrovirals for PMTCT in children born in later years.[18,63]

NRTIs used were lamivudine (3TC) and stavudine (d4T) for the majority of children as is to be expected from WHO guidelines [20]. However, several studies reported the need to use azidothymidine/zidovudine (AZT) in younger children because of its availability in syrup

formulation that does not require refrigeration.[49,53] AZT use also predominated in children started on treatment prior to the introduction of WHO Guidelines in 2004.[18,62,68]

Not surprisingly for cohorts collecting data prior to 2010, no studies reported on use of abacavir in first-line ART as this was only introduced in the WHO 2010 Guidelines.[22]

Outcomes of children on ART

Follow-up duration, mortality and loss to follow-up

Mortality and loss to follow-up (LTFU) results are summarized in Table 2. The percentage probability of dying by one year or mortality rate (per 100 child years [CY]) during the first year on ART) are reported by 13 studies and mostly fall within the range of 4-12. Notable exceptions with low mortality are the studies from Rwanda[56] and Uganda[66] with one year mortality probability of 2% and mortality rate of 1.7/100 CY, and low LTFU in both studies. These are both older cohorts with median ages of 7.2 and 6.0 years and the Rwandan cohort includes a relatively low proportion of children with WHO Stage III/IV disease (40%). Conversely a 15% percentage probability of one-year mortality was reported from a tertiary care centre in Kenya where the median CD4% at ART start was only 7% and 76% of children had been previously hospitalized,[51] and in a cohort of young children in rural Zambia.[48] Higher rural mortality (11.4/100 CY vs 5.4/100 CY during the first six months on ART) was also noted in one of the multi-site South African cohorts.[59] Mortality outcomes appear similar for studies that only report on the percentage of deaths throughout the study rather than mortality rate or probability. Notable exceptions of low mortality (2.3% deaths overall) were found in a Ugandan study of older children (median age 9.0 years) with 42% having WHO Stage III/IV disease,[55] and high mortality of 16% in the first six months in a study of children treated in a hospice setting.[65]

These outcomes are in keeping with the weighted mean mortality probability of 7.6% and rate of 8.0/100 CY calculated from 30 cohorts from resource-limited settings,[27] which is notably higher than the mean probability of 1.6% and rate of 0.9/100 CY in developed countries. Mortality outcomes in Africa appear similar to those reported from other resource-limited settings (Asia, Caribbean and South America) although within each continent there is wide variability in mortality outcomes, probably reflecting both the selection bias of children treated in particular settings and difference in mortality ascertainment.[27,85,108,109]

Estimates of two-year mortality are reported by seven studies. In comparison only two studies published prior to 2008 had sufficient follow-up to report these estimates. Nevertheless the median follow-up duration was ≤24 months in all studies, so none reported longer term outcomes. Notwithstanding, across all studies mortality probabilities by two years are very similar to those at one year.[7,8,17,18,47-49,56,57,63] Indeed almost all studies noted that mortality was particularly high in the first three to six months on ART, with the risk of death decreasing substantially in those surviving beyond this period. For example, in a South African tertiary care cohort 93% of deaths occurred in the first six months,[63] while in DRC 77% of deaths occurred within two months of ART start.[64] Mortality rates in the first three months are at least four to five times greater than those in subsequent periods.[51,58,60]

Only two studies reported on causes of death with common causes being pneumonia, septic shock, tuberculosis, gastroenteritis, malnutrition and measles.[51,64] Similar findings have been reported from studies of mortality in HIV-infected patients admitted to hospital.[40,101,106]

The interpretation of mortality outcomes reported by studies is dependent on the extent of censoring due to LTFU and the completeness and quality of mortality ascertainment.[110-112] In this respect, four studies provide no information on LTFU,[55,61,64,65] while Wamalwa *et al.*[51] exclude children with a single visit from calculations of outcome probabilities. While in some

studies LTFU is negligible,[63,66] in many the proportion of children LTFU is similar to or greater than for mortality.[18,48,49,51,54,57-60,62,67,68,113] The overall proportion of children LTFU or percentage probability of LTFU is >15% for a number of studies, however comparison of these figures is highly dependent on the way LTFU is defined by each study.[114] Since the goal of ART is to retain children alive and in care, LTFU is a negative outcome. In this respect in the AMPATH programme in Western Kenya rates of LTFU in children on ART and those not on ART were similar (14.1 and 15.2 per 100 child-years respectively),[115] however in Côte d'Ivoire loss to programme (Death +LTFU) on ART was approximately half that in pre-ART children despite similar mortality rates.[58] Differences in LTFU pre- and post-ART include both unascertained mortality and true loss to follow-up. Differences in the latter may be explained by selection bias with patients needing to demonstrate adherence to clinic appointments and other medication such as cotrimoxazole in order to be initiated on ART.

LTFU constitutes informative censoring and impacts on estimates of mortality. The few paediatric tracing studies suggest mortality amongst HIV-infected children LTFU may be very high. In rural Malawi 38% of pre-ART children and 50% of children on ART who were LTFU were found to be deceased on tracing,[116] while in Kenya the proportion of deceased children among those LTFU in a cohort of HIV-infected children mostly not on ART was 16%.[117] These estimates of mortality are generally higher than those of children remaining in care. In addition, children LTFU are more likely to have characteristics associated with mortality.[18,59,85,115] Indeed, in adults classified as LTFU in a South African ART programme where vital status was ascertained by linking to the national death registry, it was found that mortality was a major cause of LTFU with most patients' date of death being before the LTFU definition would have been met.[118] Only one study reviewed assessed the impact of unascertained mortality on overall mortality and showed that even with a modest probability of LTFU by one year on ART of 2.5%, assuming mortality in children LTFU with WHO

Stage III/IV disease increased the estimated one-year probability of mortality from 4.4 to 6.0%.[60]

Comparison of mortality across different settings also requires an understanding of the predictors of mortality and the likely impact of the characteristics of children in a particular cohort on overall mortality. The most common patient-level predictors of mortality were young age, low CD4 % or severe immunodeficiency, low WAZ/WHZ and advanced Clinical Stage, although findings across studies were not always consistent.[18,48,49,51,55,58-60,64] This may be due to substantial missing data for a number of these variables with models restricted to only a subset of all children in the cohort, or that a "missing" category had to be included as a predictor. No cohort studies found an association between viral load (VL) and mortality; however availability of baseline results was limited. In a cohort analysis of children less than two years of age initiating ART on the NEVEREST trial, mortality was associated with baseline HIV-RNA ≥750,500 copies/ml.[41] Evidence for the impact of tuberculosis at ART start on mortality is conflicting.[41,59,119] This may relate to the certainty of tuberculosis diagnosis, characteristics of children co-treated for tuberculosis and, importantly, the relative timing of tuberculosis and ART treatment. Adult studies have shown that delaying ART initiation in patients co-treated for tuberculosis results in increased mortality.[120] In a causal modelling analysis, among children co-infected with tuberculosis, there was a trend towards a harmful effect of delaying ART initiation for >60 days after starting tuberculosis treatment, especially if severely immune suppressed.[121]

Understanding programme level determinants of outcomes is challenging due to the need to account for the difference in child characteristics in particular programmes. For example, while Fatti *et al.*[59] found that rural children had higher mortality, in Zambia there was no difference in mortality between urban and rural clinics after adjustment for baseline child characteristics.[48] Similarly the lower mortality in children treated at primary health care

clinics in the Western Cape ARV Programme is ascribed to healthier children being treated in these settings.[45] In a comparison of mortality between resource-limited settings and developed countries, confounding by baseline WAZ and VL was noted.[27] Nevertheless, programme characteristics may have important impacts on outcome. For example, a number of differences in outcomes were noted when comparing children in three different settings: urban residence and facility attendance (urban); rural residence and facility attendance (rural); and rural residents attending urban facilities (rural/urban).[59] While the rural group experienced the highest mortality after adjustment for disease severity characteristics, the rural/urban group had highest LTFU and lowest probability of virologic suppression, suggesting that long travel distances adversely affected adherence. [59]

Clinical events

Two studies examined incident clinical events after ART initiation and found that 68% of children had any incident diagnosis (most commonly mucocutaneous conditions and respiratory tract infections)[54] while the probability of developing a new Stage IV disease was 5% during the first six months of treatment, with the most common Stage IV conditions being severe bacterial infections and extrapulmonary tuberculosis.[49] All incident diagnoses were most frequent in the first six months of starting ART. Despite this high incidence, studies published prior to 2008 showed that this was still lower than the incidence during the pre-ART period.[7,50]

A number of studies have specifically examined the impact of ART on tuberculosis and all demonstrate lower risk after ART initiation.[94,99,102,105,122] While most of these studies adjust for factors that might increase the risk of tuberculosis such as Clinical Stage and CD4%, only Edmonds *et al.*[105] adjust for confounding by indication whereby ART is more likely to be initiated in children who are sickest and thus at greatest risk of developing tuberculosis,[123]

and found a 50% reduced risk of tuberculosis after ART initiation. It should be noted that the incidence of tuberculosis diagnoses in the pre-ART period may be elevated in studies that specifically screen for tuberculosis as part of ART preparation or where tuberculosis programs comprise a major source of referral for HIV/ART care, while diagnoses made soon after ART start may include prevalent disease undiagnosed at ART start including unmasking IRIS events. [98] In this respect Bakeera-Kitaka *et al.*[122] showed that an apparent excess risk of tuberculosis in the first 100 days after ART start could be averted by clinical and tuberculin skin test screening for tuberculosis prior to starting ART, and that by 100 days after ART initiation risk for tuberculosis was lower than pre-ART.

CD4 response

CD4 values show marked increases on ART in the 11 studies which report on these. Increase is most rapid in the first six months on ART with median/mean CD4% increases of 11.3% and 12.6% reported, [48,62] resulting in cohort median/mean values >20% at six to twelve months in all studies, [53,56,60,62,63] sustained at longer periods.[68] Similar responses have been reported in cohorts that only include children with a particular duration of follow-up on ART.[42-44,124] Increases in CD4 absolute count in the first six months of ART for children at least five years of age range between 200 and 300 with cohort mean/median values >500 cells/mm^3 by six months after ART initiation among children in this age group.[42,44,53,55,56,60,67] Median/mean increases >600 cells/ are seen in younger children.[42,67] No differences have been noted in CD4 responses on ART between resource-limited and wealthy countries, although mean values reached at six and twelve months are lower in resource-limited settings due to lower values at ART initiation.[27,44]

In a detailed study of the pattern and determinants of CD4% response, it was noted that while before ART CD4% declined at 0.64% per year, there was a steep increase of 6.2% per year

after ART initiation with less brisk responses in older children and those with higher VL at ART initiation. There was no difference between children treated with NNRTI or PI. CD4% values tended to plateau at 23% overall, but were higher in younger children and those completely suppressed throughout ART.[125] In contrast, in a study aimed at identifying predictors of mortality and viral response after the first six months on ART, gain in CD4% was stable across all age groups.[42] The detailed description of CD4 responses in the latter study highlights that while median/mean CD4% increases may be brisk, approximately 10% of children experience no increase in CD4%, and values may even decline.[42]

Growth response

Seven studies published between 2008 and 2010 provided some information about changes in WAZ, and two studies about changes in HAZ. All studies noted increased mean/median WAZ on ART with a pattern similar to that of CD4% with an early steep increase, followed by slower increases thereafter.[48,56,59,61,63,67,68] In Côte d'Ivoire, WAZ declined pre-ART at a rate of 0.31% per year, but increased at a rate of 0.61% per year after ART start.[125] In a detailed study of growth trajectories during the first two years on ART in Malawi, the steepest early increases were noted in children with the lowest baseline WAZ.[68] In a study of children remaining in care for at least six months, weight gain on ART was faster than reference values from a healthy population, suggesting catch-up growth.[42] This study also showed the slowest weight gain was in children four years of age, with faster gains in infants and younger children as well as those approaching adolescence.[42] Naidoo *et al.*[61] noted that only children who were moderately and severely underweight showed improved nutritional status on ART. The fastest WAZ change in all studies of +1.16 units during the first six months on ART was seen in a very young cohort (median age 31 months), although there may be selection bias in the follow-up measurements as more than 20% of children were

LTFU by six months. Similar rapid WAZ increases were seen in a cohort analysis of children prior to randomization on the NEVEREST trial.[98]

There were no differences noted in the rate of WAZ improvement between urban and rural children, however mean/median values at baseline and throughout follow-up were lower in rural children.[48,59] In a comparison of growth on ART between children in Uganda and the UK, initial growth response in Uganda was slow with a median decline in WAZ over the first six months, but increased thereafter.[44] There was also wider variation in weight increase in Uganda.[44] Like the urban/rural comparison, there was no difference in rate of WAZ improvement, but because of much lower baseline WAZ scores in Uganda, a much greater proportion of children in Uganda were underweight throughout follow-up compared to in the UK.[44] Indeed, in Malawi it was noted that in children who start ART with a baseline WAZ $\leq$-2, which comprise a substantial proportion in many African cohorts, normal WAZ values are not attained even by 24 months on treatment.

Increases in HAZ were noted in both cohort studies that reported this,[67,68] but were slower and lagged behind WAZ increases. Yotebeing *et al*.[42] found height gain on ART to decrease with increasing age. In the UK/Uganda comparison there were again no differences in rate of HAZ increase between the two countries, but a much greater proportion of children with stunting in Uganda both at ART start and follow-up.[44] Although the duration of this study was too short to assess long term growth patterns, if results are extrapolated throughout childhood, the average 17-year-old boy (girl) would be 1.72 (1.60)m tall in the UK, compared with the general UK population average of 1.76 (1.64)m and only 1.53 (1.47)m in Uganda, a deficit of around 20 cm compared with HIV-infected counterparts in the UK.[44]

There are several possible explanations for the poor growth in HIV-infected children including acute illness, poor dietary intake, malabsorption, and increased energy use during

illness and to support HIV replication.[39] In resource-limited settings, poor food security and delayed access to health care and ART may contribute to poorer nutritional status both at ART initiation and thereafter. High dose micronutrient supplementation has not been shown to improve mortality, immunological or growth outcomes in HIV-infected children irrespective of ART use, but earlier initiation of ART in severely malnourished children results in better outcomes compared to deferring ART.[126,127]

Table 2: Follow-up duration and outcomes of children in studies of paediatric ART outcomes published from 2008-2010.

Study	Median (IQR) follow-up duration (months)	Percentage deaths	Percentage loss to follow-up	Percentage transferred out	One-year percentage probability of death (95%CI)	One-year percentage probability of loss to follow-up (95%CI)	One year mortality rate (per 100CY) (95%CI)	One year LTFU rate (per 100CY) (95%CI)	Median (IQR) CD4% gain at one year	Percentage viral load <400 copies/ml at one year
Kids ART-LINC Collaboration 2008	20.3 (11.7-27.9)	6.4	7.8	7.7	6.0 (5.0-7.1)	5.0 (4.1-6.1)	NR	NR	NR	NR
Barth *et al.* 2008	all at least 12 months potential FU	9	17	NR	NR	NR	NR	NR	17.6 (14.1-21.1)	71
Jaspan *et al.* 2008	PI 12.9 (3.6-23.2); NNRTI: 32.8 (16.7- 40.0)	7.2	2.3	NR	7.6 (5.2-10.8)	1.3 (0.5-3.4)	NR	NR	NR	54
Kiboneka *et al.* 2008	12.4	2.3	NR	NR	NR	NR	NR	NR	5.8[c]	83[f]
Van Griensven *et al.* 2008	24 (14.4 - 31.2)	2.6	3.8	9.5	2.0	3.0	NR	NR	NR	NR
Van Winghem *et al.* 2008	16.3 (7.2-26.4)	4.9	10.2	16.1	4.7	NR	NR	NR	NR	NR
Callens *et al.* 2009	17.7 (14.0-23.7)	10.4	NR	NR	10.4 (7.4-14.5)	NR	11.6 (7.9-16.4)	NR	NR	NR
Harding *et al.* 2009	NR	16	NR	NR	NR	NR	NR	NR	NR	77[d]
Mubiana *et al.* 2009	9.2 (3.6-15.1)	NR	NR	NR	NR	NR	7.0 (5.5-8.8)	13.6 (11.4-16.0)	NR	NR
Ntanda *et al.* 2009	non orphans 14.0 (9.0-26.0) orphans 15.0 (8.0-26.0)	3.0	6.9	NR	NR	NR	1.66	NR	NR	NR
Nyandiko *et al.* 2009	NR	6.0[a]	19	NR	NR	NR	NR	NR	NR	NR

Study	Median (IQR) follow-up duration (months)	Percentage deaths	Percentage loss to follow-up	Percentage transferred out	One-year percentage probability of death (95%CI)	One-year percentage probability of loss to follow-up (95%CI)	One year mortality rate (per 100CY) (95%CI)	One year LTFU rate (per 100CY) (95%CI)	Median (IQR) CD4% gain at one year	Percentage viral load <400 copies/ml at one year
Anaky *et al.* 2010	NR	12.3	11.6	5.5	NR	NR	14.4 (11.7-17.2)	months 1-3: 53.1 (43.2-63.0) months 4-12 13.7 (10.5-17.0);	NR	NR
Fatti *et al.* 2010	censored at 24 months	3.0	7.7	NR	urban 3.4 (2.4-4.8) rural 7.7(4.5-13.0) urban/rural 3.1 (1.7-5.6)[b]	urban 11.5 (9.3-14.0) rural 8.8 (4.5-16.9) urban/rural 16.6 (12.4-22.6)[b]	NR	NR	12.0 (7.0-17.6)	81[d]
Germenaud *et al.* 2010	all at least 6 months potential follow-up	9	21	NR	NR	NR	NR	NR	NR	56
Janssen *et al.* 2010	NR	6.7	3.8	2.5	NR	NR	4.4[c]	2.5[c]	NR	74
Naidoo *et al.* 2010	NR	5.0	NR	NR	NR	NR	NR	NR	NR	76[b]
Sauvageot *et al.* 2010	10.5 (3.7-20.6)	6	10	8	7 (6-8)	8	NR	NR	NR	NR
Sutcliffe *et al.* 2010a	NR	6.9[d]	8.8[d]	7.3[d]	NR	NR	NR	NR	approximately 12.5%	NR
Sutcliffe *et al.* 2010b	urban 13.7 (3.8-29.3) rural 7.6 (2.9-16.3)	9	NR	NR	NR	NR	6.9 (5.4-9.1)	NR	14.4 (9.5-21.0)	NR
Wamalwa *et al.* 2010[e]	21 (6-33)	13	7	4	15	NR	8.4[c]	NR	NR	NR
Weigel *et al.* 2010	23.4 (11.1 - 33.7)	4.3	28.2	27.4	NR	NR	NR	NR	NR	NR
Bock *et al.* 2009	NR	NR	NR	NR	10.3 (8.1-12.8)	4.3 (2.9-6.1)	NR	NR	NR	73
Boulle *et al.* 2009	NR	11.5	4.3	11.3	NR	NR	NR	NR	NR	NR

NR Not reported; [a]includes children not on ART; [b]by 24 months on ART; [c]throughout study; [d]by 6 months on ART; [e]excludes children with only 1 visit; [f]at 18 months

Virological suppression

Eight studies reported on the proportion of children that achieved viral suppression (usually defined as HIV-RNA<400 copies/ml), and all except one[56] were from South Africa, reflecting inclusion of HIV-RNA in routine monitoring in this country, which is unusual for resource-limited settings. The proportion of children with viral suppression at 6, 12 and 24 months was >70% in all studies, except in the young tertiary care cohorts in Mali and Cape Town.[63,67] In Cape Town (median age 26 months) 54% and 59% of children were suppressed at 6 and 12 months on ART.[63] In this study children were less likely to attain suppression if treated with NNRTI-based (mostly NVP-based) compared to PI-based regimens (adjusted OR: 0.38), with 71% and 61% of children on PI-based therapy attaining suppression at 12 and 24 months respectively. In a cohort analysis of the NEVEREST trial with all children initiating PI-based ART at less than two years of age, the probability of suppression by 39 weeks on ART was 71% overall, but significantly lower in children co-treated for tuberculosis.[41] IRIS events were also associated with failure to suppress.[98]

Poorer virological suppression on NNRTI-based therapy could be due to previous exposure to NVP for PMTCT, however the P1060 study recently reported poorer virological outcomes with NVP-based first-line ART irrespective of prior PMTCT exposure.[128-130] The proportion of children with previous PMTCT exposure in the Cape Town cohort was not reported, although most children with PMTCT exposure would have received dual therapy.[63] Notwithstanding, in Uganda >75% of children treated with NVP-based regimens achieved suppression irrespective of prior exposure to sdNVP, however at least six months had lapsed between sdNVP exposure and ART initiation. In the absence of baseline resistance, poor adherence is the most likely cause of failure to achieve suppression, and PI-based regimens may be more forgiving of non-adherence with a higher barrier to resistance.[63,131] For example, in a sub-study in the same Cape Town cohort, 77% of children on LPV/r-based

regimens achieved suppression, despite only 64% having adherence >80% based on electronic measurement of adherence.[131] Lower viral suppression rates in rural children treated at urban health care facilities in South Africa are ascribed to poor adherence due to difficulties in regularly collecting treatment for families with long travel distances to clinics.[59] In contrast, Bock *et al.*[45] found no difference in viral suppression between children treated at PHC clinics compared to secondary and tertiary hospitals.

In the Uganda/UK comparison of treatment outcomes, similar proportions of children were suppressed in both countries at both six and 12 months on ART,[44] and, while a review found a lower proportion of children achieving suppression in developed countries compared to resource-limited settings, this was not significant.[27] Comparisons of viral efficacy between cohorts are challenging due to discrepancies in whether outcomes are reported on an intention-to-treat (ITT) compared to an "as treated" basis, selection bias if HIV-RNA is not measured on all children and uncertainty with respect to whether children are treatment naïve at ART start or not. For example, Barth *et al*.[62] report that 53% of children had HIV-RNA <400 copies/ml using ITT analysis, compared to 71% in an "as treated" analysis. Similarly, 61% of children were defined as having virological failure when defined as HIV-RNA >400 copies/ml or LTFU or death by six months on ART, but nearly one-third of this group was made up of children LTFU/deceased.[67] Selection bias may be important as studies done in the context of routine HIV-RNA monitoring report up to 40% of missing data on HIV-RNA at a particular monitoring time-point.[60]

Virological failure, resistance and strategies for measuring treatment success

While only one of the cohort studies systematically reviewed reported on virological failure (VF), there have been a few studies from resource-limited settings examining VF, resistance and the role of different monitoring strategies. Most studies define VF on the basis of a single

elevated HIV-RNA measurement[38,43,67,84] or are cross-sectional surveys of patients in care at a particular time point,[132,133] reflecting limited access to routine monitoring needed to determine confirmed VF. In the two studies where failure is based on confirmed elevated HIV-RNA measurements, 17% of children had sustained viraemia beyond 24 weeks on ART,[134] while the probability of either failing to suppress to <1000 copies/ml after 12 months on ART or having two consecutive measures >1000 copies/ml after initial suppression was 5.5% by 24 months and rose to 30.1% by 36 months.[42] In studies where failure is based on a single HIV-RNA measurement above threshold, the proportion of patients with failure after one year on ART is 20-30%,[38,84,124] except in the Côte d'Ivoire cohort where 51% had a single HIV-RNA >1000 copies/ml at one year on ART.[43] The latter study included a small number of children on dual therapy, 67% on nelfinavir-based ART and nearly half the children had evidence of poor adherence.[43] Two cross-sectional studies of viral efficacy reported VF (>400 copies/ml) in 32% of children after a median of 28 months on ART[132] and 58% after a median of 40 months on ART.[133] In the latter study, however there was no access to second-line therapy, whereas in the former 12% of children were on second-line regimens. The proportion of children diagnosed as failing therapy is thus higher in cross-sectional studies or those based on unconfirmed elevated measurements as confirmation of elevated HIV-RNA after re-inforcement of adherence is critical to exclude poor adherence as a cause of the raised HIV-RNA. It has been argued that VL monitoring can be an important tool to discriminate between poor adherence and therapeutic failure.[135,136] In the Rwandan cohort, nearly one third of children noted to have HIV-RNA >400 copies/ml after 18 months of ART and in whom a subsequent measurement was performed, resuppressed at subsequent measurement.[56]

In the few studies examining child characteristics at ART start that predict non-suppression or VF, the most consistent finding is an increased risk in infants and younger children, and

those with low CD4% or count.[63,84,132,137] Studies also consistently show a higher risk of failure in children on NVP-based compared to EFV-based regimens.[38,84,132]

Since access to routine HIV-RNA monitoring remains poor in many resource limited settings, the utility of other readily available measures to identify children failing therapy has been examined. Current and previous WHO[20,22] or US Department of Health and Human Services (DHHS)[138] clinical and immunological failure (IF) criteria have very low sensitivity for identifying VF in children.[38,132,134] Emmet *et al*.[132] showed that if one added physician documented maladherence and CD4%<25 to these criteria then sensitivity increased to 57% but specificity dropped to 70%. While low sensitivity may result in leaving a child on a failing first-line regimen, low positive predictive value (PPV) is also a concern as children who are actually virally suppressed may be inappropriately switched to expensive and limited second-line regimens. PPV of IF criteria for diagnosing VF as low as 16% has been reported.[38]

Studies of alternate surrogate markers for VF show an increased risk in patients with low CD4% or WAZ increase on ART.[42,67] For example, there is increased risk of VF associated with weight or CD4% gain <33rd centile.[42] Emmet *et al*.[132] report that a single decline of CD4 count by >30% between measurements or two declines of >10% over consecutive tests is associated with VF in children >5 yrs old at study enrolment. However the sensitivity, specificity and predictive values of these measures for accurately identifying VF have not been assessed.

The key reason for identifying VF in addition to IF is to prevent accumulation of resistance mutations that might compromise effectiveness of second-line therapy. The reported proportion of children with at least 1 primary mutation among those failing NNRTI-based therapy is high, ranged from 69% and 73% in studies of children with a single elevated HIV-

RNA after six to twelve months on therapy[43] to nearly 100% at longer durations on ART.[124,133,139,140] Resistance was rare in those defined as failing with HIV-RNA between 400 and 1000 copies/ml, but very common in those with HIV-RNA >1000 copies/ml, suggesting that there may be an important opportunity to prevent resistance with improved adherence interventions in those with small HIV-RNA blips.[67]

Mutations conferring resistance to NRTI (M184V) and NNRTI (frequently Y181C) were approximately equally common, with thymidine analogue mutations (TAMs) being less frequent and only one study reporting PI mutations,[140] only one of which conferred resistance. However, only the Côte d'Ivoire study included a substantial proportion on PI-based therapy. Nevertheless, distinguishing between poor adherence and true VF in children on PI-based therapy may be challenging and require resistance testing, especially if there is prior exposure to unboosted ritonavir.[141] In Côte d'Ivoire, the estimated one-year probability of developing any class resistance mutation was 44% - 15% for those with continually undetectable HIV-RNA; 63% in children with detectable HIV-RNA but >0.5 $\log_{10}$ decline, and 95% if there was no virological response.[43] The rate of TAM accumulation in children remaining on a non-suppressive regimen has been estimated at 0.59 per year.[124] Not surprisingly resistance was associated with poor adherence[133] and poorer CD4 response,[124] while the Y181C mutation was more common in those with prior exposure to sdNVP although this mutation was rare at ART initiation.[124]

1.3.5 Summary

With more than 40 studies published by the end of 2010 reporting outcomes for children on ART, there is now substantial data supporting mostly low mortality on ART with good growth, CD4 and viral responses. However, while overall mortality is low, early mortality is substantial due to children mostly starting ART with advanced disease, and high rates of

LTFU reported in some studies may hide unascertained mortality. Similarly the capacity to attain normal CD4 and anthropometric measures may be attenuated due to delayed access to ART. While increasing reported cohort size for multi-country and multi-site studies in comparison to studies published prior to 2008 suggests expanding access to ART, the median age of children at ART initiation is still high outside of tertiary care settings, indicating delayed ART initiation. Similarly, while there has been some improvement in disease severity characteristics in studies published after 2008 in comparison to earlier studies (for example, median CD4%, proportion with WHO Stage III/IV disease), such improvements are modest. Indeed, for many markers of disease severity such as WAZ, HAZ and median HIV-RNA, there has been little change over time in the characteristics reported from published studies. The extent to which children are starting ART earlier since revisions to WHO guidelines advising earlier access to ART and impact of this on ART outcomes needs to be examined.[21,22] Outcomes and determinants of outcomes reported by a particular cohort frequently reflect the selection bias of patients treated in that setting (e.g. level of care; rural or urban) and there is a need to examine overall outcomes and determinants across a range of well characterized settings and assess their generalizability. There remains very little data on longer term outcomes (>24 months) on ART.

While the probability of VF is low in most studies, there are few studies with failure definitions based on confirmed elevated HIV-RNA measurements and most are short-term and in children treated exclusively with NNRTI-based regimens. Nevertheless the poor access to HIV-RNA monitoring, low diagnostic accuracy of non-HIV-RNA measures for detecting VF and high proportion of resistance mutations in children remaining on non-suppressive therapy are concerning as more children are on ART for longer periods in a context of limited access to alternative regimens.[36]

1.4 The IeDEA-Southern Africa Collaboration

1.4.1 Background

The global International epidemiologic Databases to Evaluate AIDS (IeDEA) network (www.iedea.org) is an international research consortium established in 2005 by the National Institute of Allergy and Infectious Diseases (NIAID) to provide a rich resource for globally diverse HIV/AIDS data. IeDEA Southern Africa (IeDEA-SA) is one of seven IeDEA regional collaborations that are part of the IeDEA network. HIV care and treatment sites that are part of IeDEA-SA and other IeDEA regions collaborate to collect and define key variables, harmonize data, and implement methodology to effectively pool data to generate large data sets to address unique and evolving research questions in HIV/AIDS clinical care and epidemiology that are unanswerable by single cohorts.

IeDEA-SA built upon early experience with the Antiretroviral Therapy in Lower Income Countries (ART-LINC) and the paediatric KIDS-ART-LINC Collaborations of HIV cohorts.[18,142,143] At inception in 2005, the overarching aims of IeDEA-SA were to conduct clinical, epidemiological and health services research in order to inform HIV/AIDS service delivery in southern Africa, to increase the capacity for delivering ART and, ultimately, to improve the prognosis of people living with HIV in southern Africa. IeDEA-SA successfully recompeted for funding in 2011. Specific aims of the recompetition proposal that are relevant to this project are:

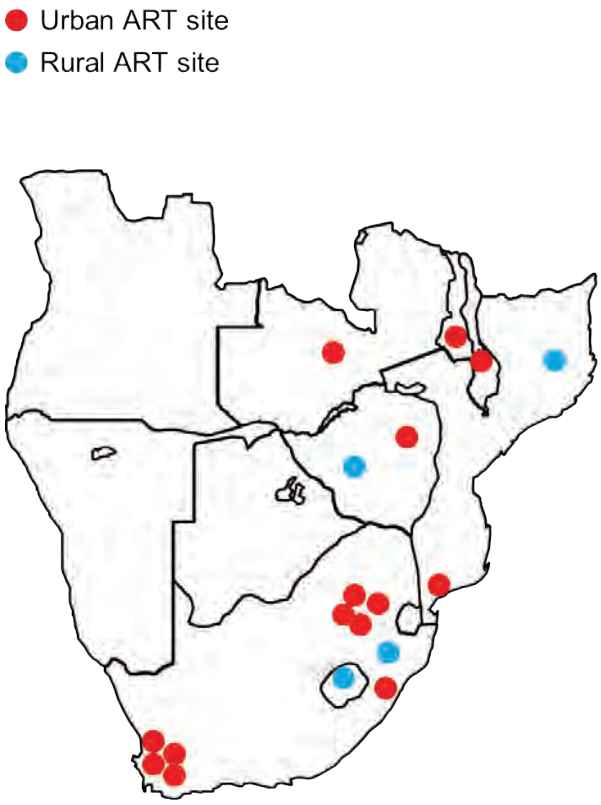
- To continue to provide the best available data related to the delivery of ART in children and adolescents in Southern Africa, with a focus on long-term programme effectiveness and outcomes.
- To describe the long-term and temporal trends in regimen durability and tolerability and examine monitoring strategies.

1.4.2 Structure of the IeDEA-SA Collaboration

IeDEA-SA is co-ordinated by a partnership of data centres at the University of Cape Town (UCT), South Africa and the University of Bern, Switzerland. The PhD candidate was the lead paediatric analyst at UCT from 2007–2011. Since 2011 she has been joint Principal Investigator of the project together with Professor Matthias Egger from the University of Bern. The number of IeDEA-SA collaborating cohorts has changed since inception, based on ability and willingness to contribute data and provide scientific input into combined analyses. By the end of 2012, IeDEA-SA was a collaboration of 18 cohorts in 6 countries, as illustrated in the map of IeDEA sites (figure 1) below, with data on more than 300,000 HIV-infected adults and 35,000 HIV-infected children ever started on ART. Cohorts provide HIV care and treatment for either adults only, infants and children only, or both.

1.4.3 Data management and harmonization

IeDEA-SA has mostly not collected *de novo* data but relied on existing electronic routine individualized data collection at collaborating cohorts. In order to participate, cohorts needed to electronically capture a minimum of sociodemographic, clinical, laboratory, and pharmacological data. Clinics have used a variety of software for collecting their data, including Fuchia™,TherapyEdge™, Trachealth™, Microsoft Access™, EpiInfo™ and in-house software, and data are easily exportable from these databases.



Lesotho
SolidarMed, Lesotho
Malawi
Lighthouse clinic, Lilongwe
Queen Elizabeth Central Hospital, Blantyre
Mozambique
SolidarMed, Mozambique
CISM, Manhica
South Africa
Aurum Institute, Johannesburg
Thembalethu Clinic Cohort, Johannesburg
Khayelitsha ART program, Cape Town
Red Cross Children's Hospital, Cape Town
Tygerberg Hospital, Stellenbosch
Gugulethu ART program, Cape Town
McCord Hospital, Durban
Harriet Shezi, Soweto
Rahima Moosa, Johannesburg
Hlabisa HIV Treatment Program, Hlabisa
Zimbabwe
Newlands Clinic, Harare
SolidarMed, Zimbabwe
Zambia
CIDRZ, clinics countrywide

Figure 1: Map of ART sites.
Note: urban sites denoted by red on the map and normal font in the list; rural sites denoted by blue on the map and italic font in the list.

The PhD candidate led the development of the first version of the IeDEA-SA Data Transfer Protocol (DTP) in 2008 together with data managers and other staff from the data centres, as well as the collaborating sites. The IEDEA-SA DTP provides the format and structure for the collaborative IeDEA-SA database and for data imports from site databases into the IeDEA-SA database. It was based on the HIV Cohorts Data Exchange Protocol (HICDEP) (www.hicdep.org) used by EuroCoord, a network of the biggest HIV cohorts and collaborations in Europe. A key role of the PhD candidate was to modify the HICDEP format for resource-limited settings and adapt it appropriately to collect paediatric data. The candidate has been involved in all subsequent revisions of the DTP, which has become the

South African Data Exchange Standard for all data transfers between HIV monitoring software programmes in the country.

The following types of data are collected in the IeDEA-SA DTP (subject to availability) and stored in six core tables and five optional tables as follows:

CORE TABLES

PAT: Demographic and clinical data on patients, clinical characteristics at start of ART in ART-treated patients, as well as information on the outcomes of patients.

LAB: All laboratory tests including CD4, HIV-RNA, safety monitoring tests, opportunistic infection diagnostic tests.

ART: data on all antiretroviral drugs that a patient has received or been exposed to including PMTCT (both exposure to mother as well as infant peri- or post-natally) or post-exposure prophylaxis.

OI: information on all opportunistic infections or incident HIV-associated diagnoses.

VIS: data on all clinical visits (including the first visit at the facility). Data includes weight, height, and treatment with prophylactic drugs such as cotrimoxazole and isoniazid.

META: key characteristics of the data that is transferred.

OPTIONAL TABLES

LINK: information on family members (partners, children and siblings) also receiving HIV care either within the cohort or at another site so that these records can be linked.

PREGNANCY: information on all pregnancies, including spontaneous abortions/miscarriages and terminated pregnancies, and their outcomes.

*PAR_HEALTH***:** information on parental health status for patients 15 yrs or younger.

*TUBERCULOSIS***:** information on all episodes of tuberculosis.

TRIAL: information on enrolment in a trial or research study (apart from cohort analysis of routinely collected data) on which a patient is enrolled.

Patient data is transferred anonymously from sites to the IeDEA-SA data centres at the Universities of Bern (sites from outside South Africa) or Cape Town (South African sites) at regular intervals using the IeDEA-SA DTP. Data managers at the data centers merge these data sets into a single IeDEA-SA Microsoft SQL Server database that is stored on a secure server at each data center, with access only to the data managers. The first data merge was completed in 2008 and four papers in this thesis use data from that merge.[144-147] The remaining two papers use data from later merges.[148,149]

All analyses included in this thesis used data from the combined IeDEA-SA dataset which was extracted via open database connectivity (odbc) download to STATA (versions 10-12, College Station, Texas) of the relevant tables from the IeDEA-SA DTP. The candidate performed all data management needed to create analysis-ready datasets including merging of data from the different tables, quality checking and data cleaning in consultation with contributing sites, calculating loss to follow-up based on site database closure dates, calculation of anthropometric z-scores using WHO standards[150] and development of programming algorithms, for example, to extract data at particular intervals at or after ART initiation, identify instances of treatment interruption, virological and immunological failure and switching to second-line therapy,

IeDEA-SA also collected data on characteristics of clinics and treatment programmes using a site assessment questionnaire on the WHO DataCol platform. This data was used to describe the characteristics of sites in these analyses.

1.4.4 Funding

IeDEA-SA has been funded by the National Institutes of Health (NIH) since 2006, with NIAID being the primary funding agency. Throughout the project, the Eunice Kennedy

Shriver National Institute of Child Health and Human Development (NICHD) and the National Cancer Institute (NCI) have co-funded IeDEA to support the inclusion and analysis of patient data on infants, children, adolescents, and pregnant women as well as cancer respectively.

1.4.5 Ethics

The IeDEA-SA study (previously known as the Observational Antiretroviral Studies in Southern Africa [OASIS] Collaboration) has ethical approval from the UCT Health Sciences Faculty Research Ethics Committee (HREC REF: 084/2006) which has been renewed annually. Each cohort has institutional ethical approval to contribute data to IeDEA-SA analyses.

1.4.6 Procedure for use of data and conducting analyses

While the IeDEA-SA data are held in a combined dataset at the data centres, ownership of the data remains with the contributing cohort, with the data centres acting as custodians of the combined dataset. To use data for an analysis, investigators must propose a concept sheet outlining the analysis and outputs. The concept sheet is circulated to all site investigators as well as the data centres for approval. For each concept sheet, sites may choose to have their data included or excluded at the concept approval stage, but not once the analysis results are available. For each of the analyses included in this thesis, the PhD candidate was responsible for developing, circulating and finalizing the concept sheet and ascertaining which sites wished to participate in each analysis.

CHAPTER 2:
RESULTS IN THE FORM OF PUBLISHED PAPERS AND PAPERS SUBMITTED FOR PUBLICATION

2.1 Paediatric antiretroviral treatment programmes in sub-Saharan Africa: a review of published clinical studies

Paper overview

This is a systematic review of the characteristics and outcomes of studies of paediatric ART programmes published prior to 1 January 2008. It forms part of the literature review and provides the background and context of the study at the time it was first conceived. It has been supplemented by a further more detailed literature review of papers published from 2008 to 2010 in chapter 1, section C.

Contribution to the thesis and novelty

Together with the updated literature review, this paper addresses the first objective of the thesis, and provides background to the subsequent analyses undertaken. While other analyses of paediatric ART studies from resource-limited settings have been published,[13,27] this includes a review of characteristics of paediatric ART programmes, such as staffing, funding sources, eligibility criteria and drug regimens and formulations used. This highlighted heterogeneity in ART programmes and the finding that the good outcomes of paediatric ART programmes in Africa have been achieved despite enormous health service and drug access constraints. Heterogeneity in programme and child characteristics are a key feature in the analyses included in this thesis, and form part of the rationale for development of a generalizable prognostic model.[148] The review also identified the need for studies of the outcomes of infants and young children initiated on ART who were not well represented in published studies, as well as studies of longer term outcomes.

Role of the candidate

The candidate was the lead investigator on this study and performed the systematic review. The candidate wrote the manuscript, incorporated input from co-authors who critically reviewed the manuscript, and submitted the final manuscript.

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Paediatric antiretroviral treatment programmes in sub-Saharan Africa: a review of published clinical studies

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Knowledge of the experience and outcomes of current paediatric antiretroviral treatment (ART) programmes in sub-Saharan Africa can inform new programmes in the region as well as enhance existing ones. This is urgently needed to facilitate the scale-up of treatment, which is needed to address the burden of paediatric HIV cases on the continent. We reviewed the characteristics and outcomes of programmes with clinical paediatric ART studies published prior to 1 January 2008. The outcomes of the studies were comparable to similar ones from developed countries; however, the duration of follow-up was relatively limited in almost all the studies reviewed. One-year survival probability was between 84% and 91%, and considerable improvement in the clinical, immunologic and viral status of the paediatric patients was generally recorded. Loss to follow-up was less than 10% in all but two studies. Adherence to treatment was good and few adverse events were reported. This is despite the fact that many programmes were subject to enormous constraints in terms of health services, and despite widespread use of adult fixed-dose combinations for paediatric patients, including young infants. While the majority of children commencing ART were severely ill, most children were old (median age >5 years for almost all studies) with relatively few infants and young children (age <2 years) receiving treatment. This is in contrast to knowledge of rapid disease progression in the majority of HIV-infected infants and despite the World Health Organization's recent recommendations to commence ART in all HIV-infected infants less than one year old. There is an urgent need to address barriers to ART for infants. Studies of the outcomes of programmes treating infants as well as those with longer-term follow-up are also needed.

Keywords: children, growth monitoring, HIV/AIDS, infants, mortality, programme assessment, survival, treatment issues, treatment practices, WHO guidelines

Introduction

The burden of paediatric HIV infections is greatest in sub-Saharan Africa, where as of December 2007 almost 90% of the world's two million HIV-infected children were living, with approximately 370 000 new paediatric infections having occurred in the preceding year (UNAIDS, 2008). In the absence of antiretroviral therapy (ART), HIV-related illnesses account for approximately 10% of childhood mortality across the continent and up to 50% of childhood mortality in southern Africa (UNAIDS, 2006; Little, Thorne, Luo, Bunders, Ngongo, McDermott & Newell, 2007). ART is highly effective in reducing morbidity and mortality in HIV-infected children in the developed world; however, until very recently, its availability to children in Africa has been limited (Patel, Hernan, Williams, Seeger, McIntosh, Van Dyke & Seage, 2008). For example, according to the most recent available paediatric ART coverage estimates, in more than half of sub-Saharan African countries, less than 15% of children needing ART were receiving it at the end of 2006 (WHO/UNAIDS, 2006). Coverage was below 35% for the remainder of the subcontinent, apart from Namibia and Botswana (WHO/UNAIDS, 2006).

Encouragingly, access to ART for children in sub-Saharan Africa is increasing, with more than 2 500 facilities providing treatment and nearly 160 000 children receiving ART by December 2007 (WHO, UNICEF & UNAIDS, 2008). Nine of the ten countries in which the vast majority of HIV-infected children live are in sub-Saharan Africa, and access to ART in these countries increased dramatically between 2005 and 2007. For example, in South Africa, Kenya, Malawi and Zimbabwe, the numbers of children receiving ART increased 2.6 times, 3 times, 4 times and nearly 5 times in that period, respectively (WHO *et al.*, 2008). The corresponding total numbers of children on ART in those countries by the end of 2007 were 32 000 (South Africa), 15 000 (Kenya), 10 000 (Malawi) and 8 000 (Zimbabwe) (WHO *et al.*, 2008).

ART provision for children in sub-Saharan Africa — with its enormous health service constraints — needs to be tailored to local circumstances. Outcomes may also be different to those in the developed world due to different socio-economic circumstances and background burden of disease. Information from observational cohorts of children receiving ART in Africa is therefore vital to demonstrate programmatic issues, such as the nature of ART provision on the continent and the effectiveness of different models

of care for children, as well as the outcomes of children receiving ART.

Since 2004, reports from isolated cohorts of children receiving ART in Africa have been published with progressively increasing frequency and greater numbers of children on treatment. To our knowledge, there is one published review of clinical studies in the medical literature demonstrating good outcomes, but with little emphasis on the characteristics of individual programmes (i.e. Sutcliffe, Van Dijk, Bolton, Persaud & Moss, 2008).

Our study was funded by the International Epidemiological Databases to Evaluate AIDS (IeDEA) Southern Africa cohort collaboration. We aimed to review published paediatric ART clinical studies in order to contextualise future paediatric ART cohort analyses, assess the feasibility of ART for children in Africa, and inform context-specific guidelines on treatment for children, as well as highlight areas for additional relevant research.

Our specific objectives were to review the following:

- The characteristics of paediatric ART programmes, in terms of funding, user fees, ART eligibility criteria and regimens used;
- The characteristics of patients at ART initiation across different programmes;
- Outcomes among children receiving ART, specifically vital status and retention in care, as well as clinical and laboratory outcomes in those who remained in care; and,
- Treatment durability and adherence.

Methods

We searched the literature through the PubMed database using the search terms 'antiretroviral children Africa' and 'antiretroviral' AND ('paediatric' OR 'pediatric') AND 'Africa.' Eligibility criteria were observational studies published prior to 1 January 2008 with a cohort including at least 25 children treated with three-drug ART and reporting on vital status outcomes. The children needed to be part of an observational cohort and not participants in an antiretroviral (ARV) drug trial. Data were extracted onto a standard form and summarised as described under the following subheadings.

Data on treatment programmes

Variables extracted from the studies included the number of facilities at which ART was provided, external funding sources, user fees, clinical care providers, availability of laboratory testing facilities, criteria used to determine patient eligibility for ART, and ART regimens used.

Patient characteristics at ART initiation

In addition to the age and gender profile of the participants in each study, disease severity was summarised using as many of the following measures as were reported: CD4 cell count and CD4 percentage (CD4%), anthropometric data reported as age- and sex-standardised *z*-scores, viral load, WHO clinical stage of disease, and opportunistic infections. The relationship of caregivers to the patients was also recorded.

Outcomes on ART

We extracted information on overall mortality and loss to follow-up (as defined by each study individually), and specifically mortality at one year in those studies where this was reported. We also noted changes in markers of disease severity, including clinical events, growth, immune and virological response. We describe treatment durability in terms of proportion of children requiring treatment changes and the reasons for this, and report on adherence for those studies where this was measured.

Results

Characteristics of the treatment programmes

Overview of the studies reviewed and their countries of origin

The characteristics of 18 studies (15 cohorts) that met eligibility criteria are shown in Table 1. Most (13 of 18; 60%) were reports from a single health facility, with three of the remainder being from multiple sites within a country and the other two being reports of the Médecins Sans Frontières (MSF) HIV programmes from multiple resource-limited countries (including non-African sites). Most reports are from southern Africa and East Africa (see Figure 1). The Malawi Paediatric Antiretroviral Treatment Group (2007) reports on national aggregate cohort data, not individualised outcomes. Two studies were reported by each of the following programmes: Agence Nationale de Recherches sur le SIDA, Abdijan, Cote d'Ivoire (i.e. Fassinou, Elenga, Rouet, Laguide, Kouakoussui, Timite *et al.*, 2004; Rouet, Fassinou, Inwoley, Anaky, Kouakoussui, Rouzioux *et al.*, 2006); Red Cross Children's Hospital, Cape Town, South Africa (i.e. Eley, Nuttall, Davies, Smith, Cowburn, Buys & Hussey, 2004; Eley, Davies, Apolles, Cowburn, Buys, Zampoli *et al.*, 2006), and the MSF multi-site cohort (i.e. O'Brien, Sauvageot, Zachariah & Humblet, 2006; O'Brien, Sauvageot, Olson, Schaeffer, Humblet, Pudjades *et al.*, 2007).

Funding and payment

Sixteen of the 18 studies report on funding sources, and 15 of these received external funding for the ART programme in addition to state health-service resources. The most common funders were the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (contributing to 25% and 31% of the studies, respectively). Eight studies acknowledged additional support for research activities.

Only McCord Hospital (in Durban, South Africa) did not provide free care and ART for HIV-infected children; rather a standard co-payment of approximately US$10 per month (irrespective of number of consultations, treatment or laboratory testing needed) was required per family receiving care (Reddi, Leeper, Grobler, Geddes, France, Dorse *et al.*, 2007). However, the provision of laboratory testing as part of routine care varied widely in the programmes reviewed. Outside of South Africa and the research settings, viral-load testing was not provided, and in some of the Malawian studies CD4 testing needed to be paid for by the patients (e.g. Ellis & Molyneux, 2007).

Table 1: Summary of the studies reviewed and the characteristics of the children at the start of antiretroviral therapy (ART) for each cohort (CD4% = CD4 percentage; HAZ = height-for-age *z*-score; IQR = interquartile range; NR = not reported; WAZ = weight-for-age *z*-score)

Study	Country	No. of sites	Observation time	No. of children on ART	Percentage females	Median (IQR) age (years)	Percentage aged <18 months	Median (IQR) CD4%	Percentage CD4 <15%	Percentage advanced stage[a]	Median (IQR) WAZ score	Median (IQR) HAZ score	Median (IQR) log viral load
Fassinou *et al.*, 2004	Côte d'Ivoire	1	2000–2002	78	44	7.2 (0.7; 15.2)[b]	5[c]	8.0 (1.9; 11.1)	NR	13	–2.02	2.03	5.4 (3.3; 7.0)[b]
Rouet *et al.*, 2006	Côte d'Ivoire	1	2000–2004	78	44	6.5 (0.7; 15.2)[b]	NR	7.5 (2.1; 11.1)	NR	NR	NR	NR	5.4 (5.1; 6.0)
O'Brien *et al.*, 2006	8 countries	multiple	2001–2005	1 184	48	7 (4.6; 9.3)	1	NR	85[d]	39	NR	–2.0 (–3.2; –1.1)	NR
O'Brien *et al.*, 2007	14 countries	26	2002–2006	568	45	3.2 (2.5; 4.1)	0	NR	79	42	NR	NR	NR
Eley *et al.*, 2004	South Africa	1	2002–2003	80	39	4.2[e] (3.5; 4.9)[f]	NR	NR	NR	94	NR	NR	NR
Eley *et al.*, 2006	South Africa	1	2002–2005	409	44	1.9 (0.7; 4.5)	51[c]	11.7 (7; 17.3)	66	99	–2.17 (–3.09; –1.12)	–2.51 (–3.41; –1.72)	5.6 (5.1; 6.1)
Jooste *et al.*, 2005	South Africa	>1 throughout province	2003–2004	100	NR	5.5[e] (0.3; 13)[b]	NR	NR	96	NR	NR	NR	NR
Nyandiko *et al.*, 2006	Kenya	9	2002–2005	279	49	6 (0.4; 13.7)[f]	7[g]	10 (1; 38)[b]	NR	NR	–2.6 (–9.6; –2.3)[f]	–2.4 (–6.1; –4.2)[f]	NR
Marazzi *et al.*, 2006	Mozambique	6	2002–?	297	NR	5.1[b] (3.2)[h]	22[c]	NR	56	NR	NR	NR	NR
Blé *et al.*, 2007	Tanzania	1	2002–2005	59	34	4.5 (0.6; 10.6)[b]	5[g]	9.6 (0; 27.6)[b]	NR	NR	–2.13 (–5.49; 2.65)[b]	–2.07 (–6.09; 4.37)[b]	NR
Reddi *et al.*, 2007	South Africa	1	2003–2005	151	51	5.7 (0.3; 15.4)[b]	NR	7.4 (2.1; 13.7)	80	70	–1.9 (–3.6; –0.9)	–2.2 (–3.0; –1.1)	NR
Song *et al.*, 2007	Kenya	1	2003–2004	29	47	8.5[e] (3.4)[h]	0	NR	NR	NR	–1.61[e] (1.39)[h]	NR	5.1[e] (0.7)[h]
Wamalwa *et al.*, 2007	Kenya	1	2004–2005	67	49	4.4 (2.4; 6.0)	NR	6.2 (3.6; 10.3)	82	NR	–2.45 (–4.3; –1.54)	–2 (–3.32; –1.04)	6.4 (6.0; 6.6)[i]
Kamya *et al.*, 2007	Uganda	1	2004–2005	250	48	9.2[e] (4.5)[h]	NR	8.6 (3.5; 12.7)	NR	89	NR	NR	5.3[e] (0.8)[h]
Malawi Paediatric ART Group, 2007	Malawi	Multiple throughout country	2004–2005	233	NR	NR	3[g]	NR	NR	NR	NR	NR	NR
Bolton-Moore *et al.*, 2007	Zambia	18	2004–2007	2 938	52	6.8 (3; 10.4)	10	11.8 (7.2; 17.4)	NR	72	–2.2 (–3.4; –1.2)		NR
Ellis & Molyneux, 2007	Malawi	1	2004–2005	238	46	7.3 (0.6; 17.6)[b]	12	NR	NR	86	–3.02 (–6.77; 0.69)[b]	–3.19 (–7.17; 0.99)[b]	NR
Bong *et al.*, 2007	Malawi	1	2004–2006	439	50	NR	2[g]	(0.1; 43.6)[b,j]	NR	NR	NR	NR	NR

[a] CDC category C disease, or WHO stage 3 or 4 disease.
[b] Range.
[c] Percentage less than age 2 years.
[d] CD4 percentage was only available for 34% of children and was only reported for children ≤59 months of age.
[e] Mean value.
[f] 95% confidence interval.
[g] Percentage less than age 1 year.
[h] Standard deviation.
[i] Children age 18 months to 3 years only.
[j] CD4 percentage given for different subgroups only, not for all patients in the cohort.

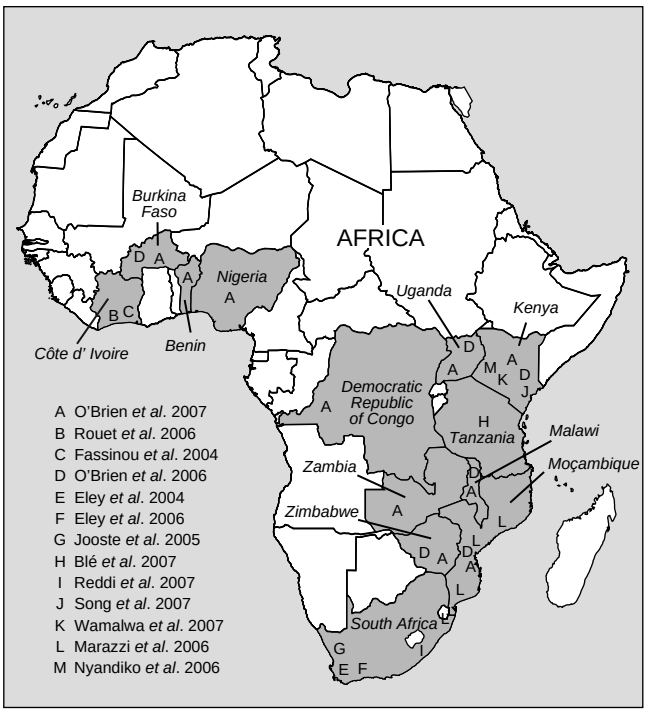

Figure 1: Map of paediatric ART sites with published studies included in the review

Providers of medical care

Half of the studies provided information on the main providers of medical care. Doctors are the exclusive providers in four of nine (44%) studies, and doctors provided care in combination with clinical officers and/or primary care nurses in another four of nine studies (44%). In a single study from Zambia, the focus for care provision was specifically from nurses and clinical officers (i.e. Bolton-Moore, Mubiana-Mbewe, Cantrell, Chintu, Stringer, Chi *et al.*, 2007). This was an explicit strategy of 'task shifting' aimed at extending the reach of HIV services and the programme successfully provided care to 4 975 HIV-infected children (2 938 on ART) via primary healthcare (PHC) facilities. This contrasts starkly to most of the other studies from hospital-based settings. Indeed, most studies that did not report on which cadre of staff provided clinical care are from hospital settings, suggesting a reliance on doctors.

Eligibility criteria for ART and the regimens used

Most of the studies used the World Health Organization (WHO) guidelines (e.g. WHO, 2004 and 2006) available at the time (or a local modification thereof) as criteria for ART commencement. Where ART was commenced prior to the publication of the 2003 WHO guidelines, the criteria in use were similar to those of WHO relating to clinical and/or immunological disease severity. In three studies, from Zambia and Malawi, access to virological testing to confirm diagnosis in children age ≤18 months was extremely limited, so presumptive diagnoses were made and treatment commenced in children with severe clinical and/or immunological disease (Bolton-Moore *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007). Ellis & Molyneux (2007) noted that in Malawi CD4 testing had to be paid for by the patient, so immunological eligibility criteria could only be considered in those who could afford testing.

The main first-line ART regimens used are shown in Table 2. Notably, four studies exclusively used adult fixed-dose combination (FDC) tablets.

Patient characteristics at the start of ART

Considering the 18 studies reviewed, a total of 7 477 children commenced ART, with the median (IQR) number per study being 236 (interquartile range: 79–381). Gender representation was essentially equal, with females comprising 49.1% of the total cohort.

Age

The median/mean age of the children ranged from 4.2 to 9.2 years, in all except two studies. One of these specifically included only children aged 18 months to 5 years (i.e. O'Brien *et al.*, 2007), while the median age of 1.9 years for the Cape Town cohort (i.e. Eley *et al.*, 2006) was markedly younger than all the others.

Where age categories are reported, it is clear that there are few infants and young children (age <2 years) on ART. Less than 12% were under 18 months old in all studies — except in one study each from South Africa and Mozambique, where 50% and 22% of children, respectively, were under age 2 years (Eley *et al.*, 2006; Marazzi, Germano, Liotta, Buonomo, Guidotti & Palombi, 2006). Overall, approximately 9.5% (650 of 6 777) of children in all cohorts of those studies reporting age category were under age 18 months.

Disease severity

The majority of children had severe disease at ART commencement (Table 1). In most studies more than 70% of children had advanced clinical HIV disease (WHO stage 3 or 4, or CDC category C) and their median/mean weight-for-age (WFA) and height-for-age (HFA) *z*-scores were well below 0. Only three studies provided data on weight-for-height (WFH) *z*-scores, with medians between –0.6 and –1.64. The median CD4% was below 10% in all but two studies, both of which included relatively larger numbers of young children (i.e. Eley *et al.*, 2004; Bolton-Moore *et al.*, 2007). Indeed, in the Zambian cohort, median CD4% declines with increasing age at the start of ART (Bolton-Moore *et al.*, 2007). Similarly, the proportion with CD4% <15% is high (≥79%) in all studies except those including many young children (i.e. Eley *et al.*, 2006; Marazzi *et al.*, 2006). Only seven of the 18 studies report on baseline viral load, indicating poor access to this technology, and the median/mean $\log_{10}$ viral load ranges were high. Studies from the Northern Cape Province (South Africa) and from Mozambique reported 80% and 55% of children having >5$\log_{10}$ viral load, respectively.

Seven studies reported on current or past opportunistic infections at the start of ART. Prevalence of TB at entry into the programme was 33% in Durban, South Africa (Reddi *et al.*, 2007), and 46% in Dodoma, Tanzania

Table 2: First-line ART regimen used (d4T = Stavudine; EFV = Efavirenz; FDC = fixed-dose combination; NRTI = nucleoside reverse transcriptase inhibitor; NVP = Nevirapine; PI = protease inhibitor; 3TC = Lamivudine)

Main first-line regimen used	Study reference
Adult FDC d4T/3TC/NVP	O'Brien *et al.*, 2006; Bong *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007
2 NRTIs + NVP	Marazzi *et al.*, 2006; Nyandiko *et al.*, 2006; Bolton-Moore *et al.*, 2007; O'Brien *et al.*, 2007; Song *et al.*, 2007; Wamalwa *et al.*, 2007
2 NRTIs + EFV/PI	Eley *et al.*, 2004; Eley *et al.*, 2006; Fassinou *et al.*, 2004; Rouet *et al.*, 2006; Reddi *et al.*, 2007; Jooste *et al.*, 2008
2 NRTIs + NVP/PI	Blé *et al.*, 2007
2 NRTIs + NVP/EFV	Kamya *et al.*, 2007

(Blé, Floridia, Muhale, Motto, Giuliano, Gabbuti *et al.*, 2007). The Tanzanian cohort, however, comprised a small group of institutionalised children and it is unclear whether TB was 'active' or previous. Other studies, from Zambia, Malawi and Côte d'Ivoire, reported lower proportions (6–7%) of active TB at commencement of ART, with previous TB in 13–24% of the children (Fassinou *et al.*, 2004; Bolton-Moore *et al.*, 2007; Bong, Chen, Jong, Tok, Hsu, Schouten *et al.*, 2007). Nutritional/gastro-intestinal illnesses, fever, recurrent pneumonia and dermatitis were not uncommon.

Caregivers

Two studies from South Africa and one each from Malawi and Kenya reported on the child's main caregiver (i.e. Eley *et al.*, 2004; Reddi *et al.*, 2007; Ellis & Molyneux, 2007; Wamalwa, Farquhar, Obimbo, Selig, Mbori-Ngacha, Richardson *et al.*, 2007). This caregiver was the mother for between 38% and 79% of the children, with the greater proportion occurring in the studies that included younger children. Fathers were the primary caregivers for up to 21% of children in some studies, but for far fewer children in other settings (e.g. Eley *et al.*, 2004). Grandparents (mostly grandmothers) and other family members comprised the third-most-common primary caregivers, respectively providing care for 6–21% and 7–26% of children. Only 2–7% of the children were cared for by an institution.

Response to ART

Survival and retention in care

In all but four studies less than 10% of the children died during the follow-up period, with a maximum of 15.4% deaths in the study with the highest mortality (see Table 3). Loss to follow-up was also low (<10% in all but two studies). One-year survival probabilities are only reported by six studies and are all within a small range (0.84–0.91) (Figure 2). In general, lower probabilities of survival are seen in those studies where children were younger at commencement of ART.

Response to treatment in survivors

Clinical events

Fassinou *et al.* (2004) reported decreased incidence of pneumonia and diarrhoea after commencement of ART in children age <6.5 years from Côte d'Ivoire, with no change in older children, while Wamalwa *et al.* (2007) showed reduced hospitalisation during the six months after initiation of ART in a Kenyan programme. However, in that cohort, 58% of the children had been hospitalised during the six months preceding the start of ART.

Growth

The most consistent observation regarding growth in the 12 studies that reported this is improvement in WFA *z*-scores and/or reduced proportion underweight, with the latter being reduced by 30–80% (Eley *et al.*, 2006; Marazzi *et al.*, 2006; Ellis & Molyneux, 2007; O'Brien *et al.*, 2007). Improvement in WFH *z*-score (reduced proportion with wasting) also appears consistent across the studies, with the proportion wasted reduced to a similar degree (cf. Eley *et al.*, 2006; Ellis & Molyneux, 2007). There is conflicting data with regard to height response: three studies showed improvement, albeit smaller than for other growth parameters, while three studies showed no change. It appears that while significant improvements in all growth parameters do occur after commencement of ART, it is rare for these to normalise.

Immune response

The median/mean increase in CD4% at 12 months was between 11% and 17.5% (Table 3). Rouet *et al.* (2006) found CD4% to increase during the first 18 months on treatment and then stabilise, with better immune recovery in those children on Nelfinavir as compared to Efavirenz-based regimens. Nyandiko, Ayaya, Nabakwe, Tenge, Sidle, Yiannoutsos *et al.* (2006) similarly found CD4% to increase rapidly during the first 30 weeks of ART, after which increases were much less pronounced.

Virological response

Ten studies reported on virological outcome at varying time intervals (see Table 3). This is a relatively high proportion as viral monitoring is not routinely available in sub-Saharan Africa outside South Africa and Botswana. At one year, the proportion of children with suppressed viral load (<400 copies/ml) in most studies was between 70% and 80%, but it was strikingly lower in the Côte d'Ivoire cohort at 49% (Fassinou *et al.*, 2004). The Côte d'Ivoire cohort was the only one reporting on viral suppression beyond one year, with approximately half the children being suppressed at both age 24 months and age 36 months (Fassinou *et al.*, 2004; Rouet *et al.*, 2006).

Table 3: Summary of the study outcomes (CD4% = CD4 percentage; IQR = interquartile range; NR = not reported)

Study	Median (IQR) follow-up duration (months)	Number of children on ART	Percentage deaths	Percentage loss to follow-up	Percentage transferred out	Percentage treatment stopped or withdrawn	Percentage outcomes unknown	Median (IQR) CD4% gain at one year	Percentage viral load <400 copies/ml at one year
Fassinou *et al*., 2004	21[a]	78	11.5	5.1	NR	NR	NR	NR	49.3
Rouet *et al*., 2006	36 (30–42)	78	11.5	NR	NR	NR	NR	15.6[e]	46.5[e]
O'Brien *et al*., 2006	6 (2–12)	1 184	3	8	0	0	3	NR	NR
O'Brien *et al*., 2007	14 (7–20)	568	6	8	4	2	1	16 (11–22.6)[f]	NR
Eley *et al*., 2004	NR	80	8.8	5	0	1.3	0	NR	75[h]
Eley *et al*., 2006	12[b]	409	15.4[d]	4.6[d]	11.2[d]	2.9[d]	0[d]	NR	69.7
Jooste *et al*., 2005	6[b]	100	9[d]	3[d]	1[d]	3[d]	0[d]	NR	67[h]
Nyandiko *et al*., 2006	8 (7–10)[c]	279	3.6	11	0	0	0	11[a]	NR
Marazzi *et al*., 2006	10 (5–16)	297	9.5	4.2	0	0	0	NR	46[h]
Blé *et al*., 2007	12[b]	59	0[d]	0[d]	0[d]	0[d]	0[d]	15[a] (10.3–19.7)[c]	NR
Reddi *et al*., 2007	8 (4–14)	151	8.6	0	0	0	0	16.2 (9.6–20.3)	80.3
Song *et al*., 2007	15[b]	29	1[d]	3[d]	0[d]	0[d]	0[d]	NR	55[i]
Wamalwa *et al*., 2007	9 (3–15)[j]	67	9	NR	NR	NR	NR	11.3	67[h]
Kamya *et al*., 2007	12[b]	250	5[d]	1[d]	0[d]	0[d]	0[d]	14.7;11.3[g]	74
Malawi Paediatric ART Group, 2007	12[b]	233	13[d]	9[d]	6[d]	0[d]	0[d]	NR	NR
Bolton-Moore *et al*., 2007	12 (5–23)	2 938	6.7	13	5.4	0	0	14[a] (13.4–14.7)[c]	NR
Ellis & Molyneux, 2007	6[b]	238	8[d]	8[d]	2[d]	0[d]	0[d]	NR	NR
Bong *et al*., 2007	Variable up to 12 months	439	NR	NR	NR	NR	NR	NR	NR

[a] Mean value.
[b] Only includes children with specified number of months potential follow-up duration; all children who were not lost to follow-up, transferred out, or deceased were followed up for this duration.
[c] 95% confidence interval.
[d] Total percentage with given outcome in specified follow-up period.
[e] At 36 months.
[f] Children with baseline CD4 percentage between 5% and 15%.
[g] Children with and without viral suppression, respectively.
[h] At six months.
[i] At nine months.
[j] Range.

Treatment changes, adverse effects and failure

No studies reported specifically on the criteria used to ascertain treatment failure; however, 13 studies reported the proportion of children requiring treatment changes due to failure, toxicity or other reasons. Changes due to toxicity were minimal (<10% of children) in most studies, except the Zambian cohort where single drug substitutions were required for 17.6% of the children. Reasons for these substitutions, however, included toxicity and dosing issues (Bolton-Moore *et al.*, 2007). There were few adverse events reported in the six studies providing this data. Most common were skin rash, hepatotoxicity and anaemia. Two cases of Stephens-Johnson Syndrome occurred overall, one of which was fatal (Marazzi *et al.*, 2006; Bolton-Moore *et al.*, 2007). Switching treatment regimes due to failure was extremely rare (<5% in all studies that reported it) being highest in the Côte d'Ivoire cohort, with extended follow-up as expected (Rouet *et al.*, 2006). This is in strong contrast to the proportion of children with viral suppression in that study by Rouet *et al*. (2006): 50–70% throughout follow-up.

Adherence

Adherence to ART was measured in eight cohorts, mostly by self-report alone (four studies). Supplementary pill

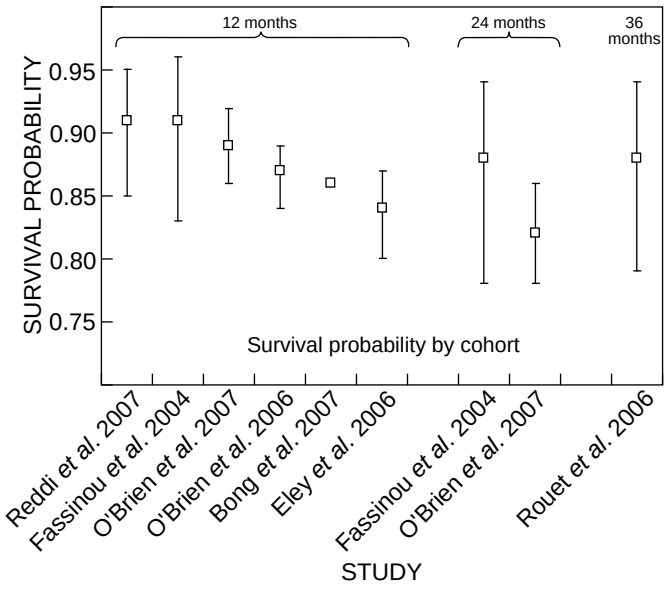

Figure 2: Summary of survival probability as reported by nine paediatric ART studies from southern Africa

counts were used in two studies, while pill counts and drug pick-up information were the primary instruments for one study each. Overall, adherence was good, with significant interruptions (more than two missed doses per month) noted for less than 11% of children in any cohort.

Discussion

This review demonstrates overwhelmingly the feasibility and effectiveness of providing ART to children in sub-Saharan Africa despite enormous health-service and socio-economic constraints. Dramatic improvements in survival, and clinical, immune and virologic status were achieved. It is difficult to make valid comparisons with studies from the developed world due to differences in socio-economic context, prior treatment experience, criteria for treatment initiation, ART regimens, and access to laboratory testing and specialist care (Patel *et al.*, 2008). For example, while viral suppression rates of 70–80% in most of the cohorts with access to viral load testing were certainly at least as good as, if not better than, those from rich countries, this may be due to the relatively older age of the children commencing ART and the fact that most children in Africa are treatment naïve (Van Rossum, Fraaij & De Groot, 2002). Nevertheless, it is notable that the good outcomes seen in these studies are similar across a range of settings, including those with limited access to ART drugs and laboratory technology as well as those where ART is not provided by doctors and care is administered from PHC facilities (such as in Zambia and Malawi) (see Bolton-Moore *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007). However, this review also highlights numerous aspects of the nature of current ART delivery in Africa, as described in the following sections.

Follow-up duration, mortality and retention in care

Due to the relatively recent availability of ART for children in Africa, follow-up periods are generally short, and long-term outcomes are as yet unexplored (except in the single small cohort from Côte d'Ivoire) (Rouet *et al.*, 2006). Nonetheless, most deaths occurred within the first few months after commencing ART, thus estimates of mortality are not likely to increase significantly, at least in the medium term. This is supported by the single longer-term study reported by Rouet *et al.* (2006) where at 42 months there were no deaths additional to those reported at 12–24 months (Fassinou *et al.*, 2004). Still, low mortality estimates should be viewed with caution in the five cohorts where short-term loss to follow-up (LFU) equaled or exceeded mortality (i.e. O'Brien *et al.*, 2006; Nyandiko *et al.*, 2006; Bolton-Moore *et al.*, 2007; Ellis & Molyneux, 2007; O'Brien *et al.*, 2007), as many of those classified as 'LFU' may have been deceased (Maskew, MacPhail, Menezes & Ruel, 2007; Krebs, Chi, Mulenga, Morris, Cantrell, Mulenga *et al.*, 2008). It is notable that all except one of the studies with this limitation were from multi-site collaborations, suggesting that it may be easier to have definite outcome ascertainment within a single site — as these may have specific patient-tracing and follow-up systems in place, or else may have made a concerted effort to ensure outcome ascertainment for the purposes of publication. Notwithstanding this, LFU in children in Africa is far lower than that of adults (Stringer, Zulu, Levy, Stringer, Mwango, Chi *et al.*, 2006). Interestingly, two cohorts (from Tanzania and Kenya, respectively) reported zero deaths and very low (3.4%) LFU (Blé *et al.*, 2007; Song, Jelagat, Dzombo, Mwalimu, Mandaliya, Shikely & Essajee, 2007). Both of these were small cohorts (59 and 29 children, respectively). The first was a residential institution for orphaned HIV-infected children with a medical doctor on site daily, while the second, in addition to providing free ART, also provided transport re-imbursement to the clinic attendees.

Age at ART initiation

The overall low mortality reported by the studies reviewed also needs to be viewed in context of the children being relatively old at the start of ART, with less than 10% overall initiating treatment before 18 months of age. In contrast, we know that HIV disease progression to death or advanced disease occurs in 50% of perinatally HIV-infected children by age 2 years (Little *et al.*, 2007). Many infants and young children in Africa clearly need but are not receiving ART. Indeed, ART-treated children in Africa represent a cohort of survivors with relatively slower progression of disease, and good outcomes are to be expected. It is not surprising that the study reporting the highest percentage of deaths after one year on treatment (15.6% mortality) is from a tertiary institution, with over 50% of that cohort having been less than age 2 years at ART commencement, and 99% of the children having advanced disease (Eley *et al.*, 2006). Yet, even in this group of very ill children, mortality on ART was relatively low.

A number of factors explain the fact that in these studies children generally commenced ART at older ages than in developed countries (Patel *et al.*, 2008). First, this reflects

the difficulty in diagnosing HIV infection in children under 18 months old where access to virologic testing is limited (Bolton-Moore *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007). This is also a consequence of poor access to appropriate ART formulations for children and the difficulty in dosing young children even where liquid formulations and refrigeration are available, due to the requirement for surface-area dosing. In fact, in Malawi, the site of three of the cohorts, all children were treated with split doses of the adult fixed-dose combination (FDC) Triomune (d4T/3TC/NVP) according to weight bands (Bong *et al.*, 2007; Ellis & Molyneux, 2007; Malawi Paediatric Antiretroviral Treatment Group, 2007), while one of the multi-country MSF cohort studies had the specific aim of demonstrating feasibility and good outcomes with use of adult FDCs in children (O'Brien *et al.*, 2006). . While the Malawian studies highlight the problems of dosing the smallest children (<8 kg) with ¼ tablet once daily (which is not recommended, as d4T should be given twice daily: WHO, 2006), Ellis & Molyneux (2007) argue that the good outcomes reported support use of this regimen due to the benefits of low cost, availability and simplicity.

Many clinicians feel inadequately trained for the perceived complicated care of the very young (Eley & Nuttall, 2007; Meyers, Moultrie, Naidoo, Cotton, Eley & Sherman, 2007). In fact, the Malawian ART scale-up programme specifically treated young children only in health facilities where paediatricians or medical doctors skilled in paediatric care were available (Ellis & Molyneux, 2007). In South Africa, paediatric care, particularly of young infants, remains centered in tertiary-care institutions (Eley & Nuttall, 2007; Meyers *et al.*, 2007).

The relative lack of young children receiving ART in Africa may also be an indication of the poor integration of HIV services for children and shortage of prevention-of-mother-to-child-transmission (PMTCT) programmes and general child health services, which although they clearly have overlapping target patient groups, are often run as separate vertical programmes within the health system. This may result in poor systems for detection and referral to ART care for HIV-infected infants and young children before disease progression. Many children with HIV infection are only diagnosed once they are severely ill, or die before an HIV diagnosis is made.

Severity of illness at ART initiation

Despite the relatively old age of children in these studies (age >5 years) and the fact that they represent survivors with slower disease progression, most children in the total cohort were severely ill at commencement of therapy. At least half of the children commencing treatment had advanced clinical disease and the median CD4% at ART initiation was low. This is in keeping with the use of WHO guidelines for treatment eligibility by most programmes. However, in the multi-country MSF cohort, the final CD4% after one year remained lower in those with greater baseline immune suppression, suggesting that immune recovery may be limited if treatment is delayed until illness is advanced (O'Brien *et al.*, 2007).

It has been suggested that the background burden of disease in Africa may exacerbate disease progression in HIV-infected children and thus complicate ART. In this regard, it is notable that two studies reported very high prevalence of TB at entry into the programme (i.e. Blé *et al.*, 2007; Reddi *et al.*, 2007). However, those figures may have been over-estimates. The difficulty of making a definitive diagnosis of TB in children, particularly when dually infected with HIV, may lead to over-diagnosis to avoid missed opportunities to treat a potentially curable opportunistic infection. Nevertheless, a high prevalence of TB in children is cause for concern. The medication burden and potential for TB immune reconstitution inflammatory syndrome (IRIS) may complicate ART (Smith, Kuhn, Coovadia, Meyers, Hu, Reitz *et al.*, 2009). Furthermore, where lopinavir/ritonavir is used in the first-line regimen for young children, concomitant TB therapy requires additional ritonavir-boosting of the regimen. Notwithstanding, in Malawi, there was no difference in survival between children commencing ART with active TB, previous TB or a non-TB diagnosis (Bong *et al.*, 2007); however, only Nevirapine (NVP)-based regimens were used, and ART was delayed until the continuation phase of TB treatment to avoid Rifampicin–NVP interactions and the risk of IRIS (Bong *et al.*, 2007).

Treatment durability

Treatment was well-tolerated with few adverse effects overall and few drug substitutions required. The rate of switching to second-line regimens was very low. This, however, needs to be viewed in the context of many of the cohorts not having access to virologic testing and/or second-line medication for children, as well as there being no current virologic guidelines for switching therapies in children (WHO, 2006). It is clear that a number of children are being maintained on first-line therapy despite ongoing viraemia, and the effects of this need to be examined in the long term. Furthermore, it would be useful to determine whether access to virologic testing has any implications for programme outcomes.

Growth response to treatment

Growth response as measured by scores for WFA and WFH was consistently good, despite probable poorer access to food in developing-country contexts, with very few programmes providing nutritional supplementation (Marazzi *et al.*, 2006). Still, the failure to attain normal *z*-score values for these parameters may reflect the residual insult of advanced disease. This is possibly also the reason for conflicting measures for growth response in terms of height-for-age (HFA), a reflection of chronic illness.

Representativeness

An important limitation of this review is that these studies may not be representative of all routine programmes across Africa. Although all are observational cohorts, many are from research settings, where care, monitoring, access to drugs and laboratory testing may be markedly better than what is available in routine services. The relatively high proportion of studies with follow-up information on patients' viral load supports this. In addition, there is a probable publication bias in favour of successful programmes; hence, the restriction of this review to published clinical studies

may have selected programmes with better outcomes. It is plausible that country-level data, programme reports, and social-science literature may portray a different picture. Furthermore, all but one of the cohorts reporting on funding had received some form of external support in addition to that from state health services, albeit through the national programme in some cases. Nevertheless, two of the studies reported on the outcomes of routine national programmes (i.e. Malawi Paediatric Antiretroviral Treatment Group, 2007; Jooste, Van Zyl, Baker, Crawford & Jassen, 2008), with one using only routinely collected data, yet their findings are consistent with those from research settings.

In addition to financial programme support, there was evidence of considerable international academic collaboration within these studies. While one-third of these published studies have both local senior and lead authorship, in an almost equal proportion (five of 16), both these roles are taken by international academics, and all except four of the publications (three cohorts) included at least one international collaborator. It is therefore possible that patient care at these sites may have been enhanced through the involvement of research institutions from wealthy countries, and thus may not be replicable on a massive scale. This also demonstrates the need to develop research and analytic capacity in sub-Saharan Africa so that lessons learned can be disseminated.

Conclusions

The feasibility and benefits of ART provision for children in sub-Saharan Africa have been clearly shown in a range of settings; however, infants and young children remain largely excluded from ART programmes, and commencement of ART occurs mostly in older children with advanced HIV disease. Emerging evidence of rapid progression of disease in children failing PMTCT regimens, and the survival benefit with early initiation of ART, has led to the revision of WHO guidelines to recommend ART commencement for all HIV-infected children under age 1 year (Mphatswe, Blanckenberg, Tudor-Williams, Prendergast, Thobakgale, Mkhwanazi *et al.*, 2007; Violari, Cotton, Gibb, Babiker, Steyn, Madhi *et al.*, 2008; WHO, 2008). There is an urgent need both to address barriers to the care of young children with HIV infection and to acquire a better understanding of the outcomes for children on ART and the determinants in this group.

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2.2 Outcomes of the South African National Antiretroviral Treatment Programme for children: The IeDEA Southern Africa collaboration

Paper overview

This paper analysed data from >6,000 children who initiated ART at one of the seven South African paediatric ART programmes collaborating in IeDEA-SA at that time. Survival, retention in care, immunological, virological and growth outcomes are described for up to three years on treatment. Associations with survival are modelled and compliance with South African National ART guidelines regarding CD4 and HIV-RNA monitoring is assessed.[151] At the time this study represented more than 20% of all children who had initiated ART across South Africa and thus reflected on the effectiveness of the national programme.

Contribution to the thesis and novelty

This paper addresses the second objective of the thesis. At the time of publication, this was the largest paediatric ART cohort from a single country setting, and remains the largest cohort to publish survival, retention in care, immunological, virological and growth outcomes for up to three years on ART using individualized data. A further unique contribution was inclusion of the largest cohort of children initiating ART at <18 months of age published at the time. Due to the large size of the cohort, inclusion of a large number of infants and young children and availability of HIV-RNA results, we were able to demonstrate independent associations between all measured markers of disease severity and mortality that had not been found in previous analyses.

Role of the candidate

The candidate was responsible for all data management to generate the IeDEA paediatric data set for analysis. She was solely responsible for the analysis. The candidate presented the analysis at the South African AIDS Conference in April 2009. She drafted the manuscript, incorporated input from co-authors and was responsible for finalising and submitting the final version of the manuscript for publication.

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Outcomes of the South African National Antiretroviral Treatment Programme for children: The IeDEA Southern Africa collaboration

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Objectives. To assess paediatric antiretroviral treatment (ART) outcomes and their associations from a collaborative cohort representing 20% of the South African national treatment programme.

Design and setting. Multi-cohort study of 7 public sector paediatric ART programmes in Gauteng, Western Cape and KwaZulu-Natal provinces.

Subjects. ART-naïve children (≤16 years) who commenced treatment with ≥3 antiretroviral drugs before March 2008.

Outcome measures. Time to death or loss to follow-up were assessed using the Kaplan-Meier method. Associations between baseline characteristics and mortality were assessed with Cox proportional hazards models stratified by site. Immune status, virological suppression and growth were described in relation to duration of ART.

Results. The median (interquartile range) age of 6 078 children with 9 368 child-years of follow-up was 43 (15 - 83) months, with 29% being <18 months. Most were severely ill at ART initiation. More than 75% of children were appropriately monitored at 6-monthly intervals with viral load suppression (<400 copies/ml) being 80% or above throughout 36 months of treatment. Mortality and retention in care at 3 years were 7.7% (95% confidence interval 7.0 - 8.6%) and 81.4% (80.1 - 82.6%), respectively. Together with young age, all markers of disease severity (low weight-for-age z-score, high viral load, severe immune suppression, stage 3/4 disease and anaemia) were independently associated with mortality.

Conclusions. Dramatic clinical benefit for children accessing the national ART programme is demonstrated. Higher mortality in infants and those with advanced disease highlights the need for early diagnosis of HIV infection and commencement of ART.

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South Africa's paediatric antiretroviral treatment (ART) programme is the largest in the world, with an estimated 32 000 children <15 years of age on treatment at the end of 2007.[1] Nevertheless the programme reaches less than half of the children estimated to need ART according to national guidelines,[2] and an even lower proportion if need is defined using revised 2008 World Health Organization (WHO) guidelines for early treatment of HIV-infected infants.[3]

Despite the size of the national programme, few individual cohorts have published treatment outcomes, with follow-up limited to 1 year.[4-6] Similar to other African countries, these cohorts have demonstrated good short-term outcomes.[7,8] However, the small size of any individual South African cohort has limited statistical power to robustly describe associations with mortality for all markers of disease severity.[9-14] Furthermore, the lack of routinely collected national monitoring data means that South Africa has lagged behind other southern African countries in publishing programme outcomes, and more importantly, has no mechanism to assess the effectiveness of this enormous health service intervention.[9,15] South Africa could potentially generate valuable paediatric ART data, not only because of the size of the programme but also due to the uniform approach to treatment shaped by national guidelines, as well as good access to laboratory testing facilities, particularly viral load.

The International epidemiologic Databases to Evaluate AIDS (IeDEA) Southern Africa Collaboration includes 8 sites in South Africa providing paediatric ART at different levels of care in 3 provinces. More than 6 000 children had commenced ART at these sites by the end of 2007, representing >20% of children in the national programme at that time. This collaboration therefore provides a unique opportunity to examine the effectiveness of the South African paediatric ART programme and the extent to which national guidelines are being followed.

Our objectives were to describe for this combined cohort the outcomes of children receiving ART, factors associated with these outcomes, and the extent to which national programme guidelines are being followed.

Methods

Study, design, setting and population

Data for this cohort analysis were collected prospectively at sites and transferred anonymously to the IeDEA data centre in a standard format between May 2007 and February 2008. Each site has institutional ethical approval for contribution of data to IeDEA collaborative analyses.

HIV-infected, ART-naïve children with known gender and date of birth who initiated treatment with at least 3 antiretroviral drugs at age ≤16 years on a documented date between 1 June 1999 and 29 February 2008 were included. Sites where less than 25 children met these criteria were excluded.

Key variables

Information describing ART programmes was provided on standardised questionnaires by site representatives. Child characteristics included measures of disease severity (WHO stage, weight, height, haemoglobin (Hb), CD4 percentage or count, viral load) at ART initiation and at 6-monthly follow-up intervals, together with initiating regimen. CD4 percentage and absolute counts are reported, with the worst of these being used to determine whether the child was severely immunosuppressed according to WHO criteria.[16] Primary caregiver and exposure to prevention of mother-to-child transmission (PMTCT) regimens were recorded.

As sites changed from the WHO 3-stage to WHO 4-stage classification of disease severity during the latter half of 2004, all children with stage 3 or 4 disease under either system were considered to have clinically advanced disease.[17] Viral loads and CD4 counts were performed by local laboratories using standard methods. A viral load <400 copies/ml was considered undetectable. Sex- and age-standardised z-scores for weight and height were calculated for children ≤10 years at time of measurement using WHO 2007 growth reference standards.[18]

Sites provided data on known deaths and transfers out (TFO). Children were deemed lost to follow-up (LFU) if the last visit date was more than 6 months before date of closure of the site database, with the last visit date used as date of LFU.

Analysis

Kaplan-Meier estimates of mortality, LFU and TFO were determined. Cox proportional hazards models stratified by site were used to assess associations between baseline characteristics and mortality. Multivariate models were built by sequentially adding the next most significant predictor variable from univariate analysis, and variables with a p-value <0.1 after adjustment for those already in the model, or that changed the hazard ratio (HR) for variables in the model by more than 10%, were retained. Separate models were generated excluding the weight-for-age z-score (WAZs) as this could only be calculated for children ≤10 years of age, and viral load, as this is not routinely available in most resource-limited settings. Since Hb at ART initiation was only available for a third of children, this was excluded from the main model, but a separate model was generated to assess the effect of anaemia on mortality. Age was categorised as <12 months, 12 - 35 months and ≥36 months. WAZs were categorised as <–3, –3 to –2 and ≥–2, according to United Nations Children's Fund (UNICEF) definitions.[19] Viral load was categorised as ≤100 000, 100 000 to 1 million and >1 million copies/ml, and year of starting ART as ≤2005 and ≥2006 as these thresholds explained the largest amount of variability in mortality. Anaemia was defined as Hb <8 g/dl.

As these data include a substantial proportion of children who received ART through donor-funded programmes before commencement of National Department of Health provision on 1 April 2004, a sensitivity analysis was performed on descriptions of baseline characteristics and survival models with data limited to those children who started ART after 31 March 2004. All statistical analyses were performed using Stata version 10 (STATA Corporation, College Station, TX).

Results

Exclusions

Of the 8 South African IeDEA sites, 1 was excluded because the cohort comprised <25 children. The remaining data included 6 266 children on ART. Of these, 85 did not meet inclusion criteria due to missing or inconsistent baseline data. Non-naïve patients (N=39) and those commenced on <3 drugs (N=64) were excluded. The final data-set therefore comprised 6 078 children (49.1% female) from 7 sites with 9 368 child-years of follow-up, and median (interquartile range (IQR)) follow-up duration of 16 (6 - 29) months.

Contributing sites

Site characteristics are shown in Table I. Of note, sites are all urban and represent major centres in 3 provinces (Western Cape, Gauteng and KwaZulu-Natal); however, all levels of care

Table I. Characteristics of facilities providing ART

Cohort name and location	Main level of care provided	Type of clinic and payment	Target population	First year of ART provision	No. of children on ART	Median (IQR) age (mo.) of children at ART initiation	Number of children (%) <1 yr of age at ART initiation
Harriet Shezi Clinic, Soweto	All levels	Public and research, free ART	Children only	2001	2 183	55.9 (21.9 - 90.3)	328 (15.0)
Rahima Moosa, Mother and Child Hospital Johannesburg	All levels	Public, free ART	Children and pregnant women	1999	1 023	44.0 (15.9 - 84.4)	202 (19.8)
Red Cross Children's Hospital, Cape Town	Tertiary	Public and research, free ART	Children only	2001	839	16.1 (6.3 - 50.2)	351 (41.8)
Tygerberg Hospital, Cape Town	Tertiary	Public and, research free ART	Adults and children, separate clinics	2000	690	21.6 (8.5 - 59.0)	240 (34.8)
Khayelitsha Community Health Centre, Cape Town	Primary	Public, free ART	Adults and children, separate clinics	2001	650	41.7 (20.3 - 74.2)	94 (14.5)
Gugulethu Community Health Centre, Cape Town	Primary	Public and, research free ART	Adults and children, separate clinics	2001	262	47.1 (18.3 - 82.4)	42 (16.0)
McCord Hospital, Durban	Secondary	Government-subsidised mission hospital, small co-payment	Adults and children, separate clinics	2003	431	72.4 (33.0 - 109.2)	33 (7.7)
Total					6 078		

are represented. There is a wide variation in the number of children being treated with ART at different sites, from >2 000 at a site providing all levels of care in Gauteng to <300 at a smaller primary care clinic in Cape Town. The median age of children from tertiary care sites is less than that of children from sites providing other levels of care (18.4 v. 51.9 months; $p<0.0001$).

Characteristics at ART start

Most children were severely ill with advanced clinical disease, immunosuppression, high viral load and impaired growth at the start of ART (Table II). The median (IQR) age of children commencing ART was 42.7 (14.7 - 82.5) months, with nearly 30% of children less than 18 months of age. The starting regimen included stavudine (d4T) and lamivudine (3TC) with either efavirenz or lopinavir/ritonavir (Kaletra) as the third drug for 81% of children.

Data were incomplete for many key variables. In particular, WHO stage was unknown for nearly a third of children, while caregiver and PMTCT exposure information was provided by only a few sites at which exposure status was still unknown for nearly 50%. Characteristics at start of ART were not substantially different when the data were limited to those initiating treatment after formal commencement of the national programme (N=5 601, results not shown).

Survival and retention in care

Mortality at 3 years was 7.7% (95% confidence interval (CI) 7.0 - 8.6%), and 81.4% (95% CI 80.1 - 82.6%) of children were alive and in care at 3 years (Fig. 1, a, b). There was rapid transfer from sites providing exclusively tertiary care to lower levels after the first 6 months of ART, with the tertiary cohort reduced by nearly 50% at 2 years (Fig. 1, c). LFU at 1 year increased from 2.2% (95% CI 1.1 - 4.7%) in those who commenced ART before 2004 to 8.2% (95% CI 7.1 - 9.4%) in those who commenced during or after 2006.

Mortality was higher for younger children, those with more advanced disease and those who were more severely immunosuppressed (Fig. 1). All markers of disease severity were independent predictors of mortality in multivariate analysis (Table III). Use of a protease inhibitor versus a non-nucleoside reverse transcriptase inhibitor as the third drug had no effect on mortality (p=0.572). Similarly, Hb <8 g/dl independently predicts mortality after adjustment for disease severity, age and programme year (adjusted hazard ratio 1.65; 95% CI 1.07 - 2.55%; p=0.024). Models excluding WAZ and viral load as predictors yielded similar results to the full model, as did models limited to those children treated after commencement of the national programme (results not shown).

Table II. Characteristics of children at ART initiation (*N*=6 078)

Year of ART start (%)	
≤2003	321 (5.3)
2004	1 076 (17.7)
2005	1 809 (29.8)
2006	1 707 (28.1)
≥2007	1 165 (19.2)
Female (%)	2 981 (49.1)
Age	
Median (IQR) age (mo.)	42.7 (14.7 - 82.5)
Less than 18 mo. (%)	1 758 (28.9)
WHO stage (%)	
1	263 (4.3)
2	745 (12.3)
3/4	3 073 (50.1)
WHO stage unknown	1 997 (32.9)
PMTCT exposure (%) (*N*=4 695)*	
Known exposed	596 (12.7)
Known unexposed	1 764 (37.6)
Exposure status unknown	2 335 (49.7)
Primary caregiver (%) (*N*=4 045)†	
Mother	2 449 (60.5)
Father	141 (3.5)
Grandmother	204 (5.0)
Other family	712 (17.6)
Other	123 (3.0)
Institution	225 (5.6)
Unknown	191 (4.7)
Laboratory measurements	
Median (IQR) CD4% by age group (*N*=4 592)	
≤11 mo. (*N*=1 045)	16.4 (10.0 - 23.6)
12 - 35 mo. (*N*=1 089)	13.0 (9.0 - 18.1)
36 - 59 mo. (*N*=712)	12.0 (7.2 - 16.5)
≥5 yrs (*N*=1 746)	10.0 (4.7 - 15.0)
Median (IQR) CD4 absolute count (cells/µl) by age group (*N*=4 852)	
≤11 mo. (*N*=1 062)	642 (280 - 1 132)
12 - 35 mo. (*N*=1 145)	636 (345 - 1 014)
36 - 59 mo. (*N*=750)	437 (251 - 691)
≥5 yrs (*N*=1 895)	435 (81 - 241)
Severely immunosuppressed (%) (*N*=4 934)‡	4 024 (81.6)
Median (IQR) log viral load (*N*=4 063)	5.36 (4.74 - 5.89)
Viral load >1million copies/ml (%) (*N*=4 063)	850 (20.9)
Haemoglobin <8 g/dl (%) (*N*=1 803)	220 (12.2)
Anthropometry§	
z-scores	
Median (IQR) weight-for-age z-score (*N*=3 892)	–1.89 (–3.20 - –0.93)
Median (IQR) height-for-age z-score (*N*= 3 690)	–2.39 (–3.37 - –1.44)
Median (IQR) weight-for-height z-score (*N*=3 186)	–0.46 (–1.73 - 0.55)
Weight-for-age z-scores (*N*=3 892)	
–3 - –2 (%)	747 (19.1)
<–3 (%)	1 096 (28.2)
Height-for-age z-score (*N*=3 690)	
–3 - –2 (%)	1 011 (27.4)
<–3 (%)	1 242 (33.7)
Weight-for-height z-score (*N*=3 186)	
–3 - –2 (%)	312 (9.8)
<–3 (%)	365 (11.5)
Regimen (%) (*N*=5 484)	
Most common regimens	
d4T+3TC+efavirenz	2 839 (51.8)
d4T+3TC+lopinavir/ritonavir¶	1 603 (29.2)
First NRTI	
d4T-based regimen	4 856 (88.5)
Third drug	
Lopinavir/ritonavir-based regimen"	1 808 (33.0)
Ritonavir-based regimen	191 (3.5)
Regimen not recorded	594

*Data only available for Rahima Moosa, Harriet Shezi, Khayelitsha and Red Cross.

†Data only available for Rahima Moosa, Harriet Shezi and Red Cross; for Harriet Shezi caregiver information was collected at first visit – may be different from caregiver at ART start.

‡WHO criteria for severe immune suppression (CD4% <25 or CD4 count <1 500/µl if age ≤11months; CD4% <20 or CD4 count <750/µl if age between 12 and 35 months; CD4% <15 or CD4 count <350/µl if age between 36 and 59 months; CD4% <15 or CD4 count <200/µl if age ≥60 months.

§Only calculated for children ≤120 months (*N*=5 535).

¶Includes 201 children with additional ritonavir boosting.

"Includes 214 children with additional ritonavir boosting.

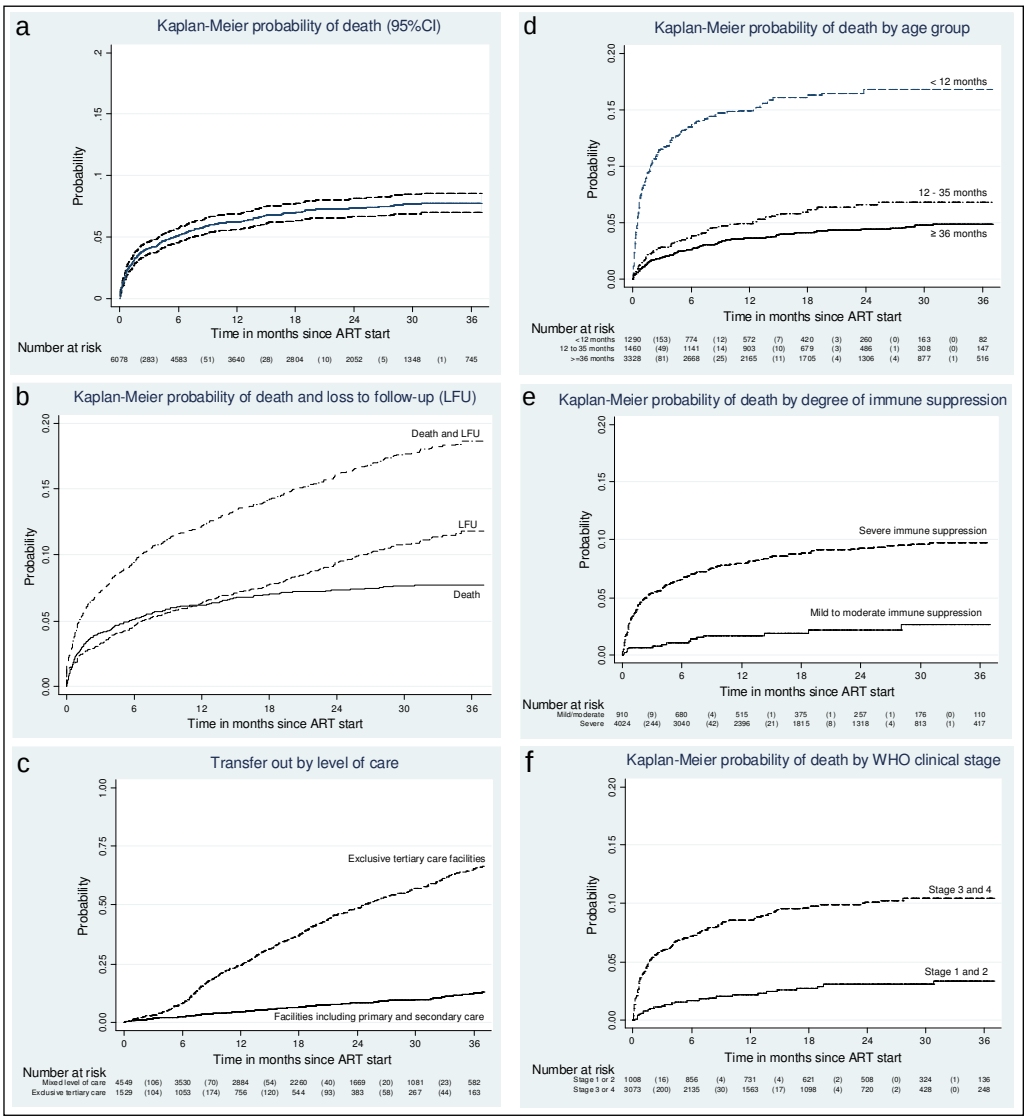


Fig. 1. Kaplan-Meier estimates for outcomes of (a) death, (b) death and loss to follow-up, and (c) transfer out. Kaplan-Meier estimates of mortality by (d) age group, (e) degree of immunosuppression and (f) WHO clinical stage.

Monitoring of viral and immune response to treatment

Follow-up measurements of CD4 and viral load are shown in Fig. 2. Notably, measurements of CD4 and viral load at 6-monthly intervals were available for over 80% and 75% of children respectively through to 36 months, with ≥80% of children virologically suppressed throughout (82.4% at 3 years; 95% CI 79.4 - 85.5%). The percentage (95% CI) of children severely immunosuppressed at 1 and 3 years dropped to 16.9% (15.4 - 18.3%) and 6.4% (4.2 - 8.6%), respectively.

Growth response to treatment

There was initial rapid weight gain from a median WAZ of –1.80 to –0.75 by 12 months, remaining relatively constant thereafter (Fig. 3). Height increased more slowly but was still increasing at 36 months, when a quarter of children still had a height-for-age z-score <–2.

Discussion

Main findings of the study

Outcomes of this cohort of ART-treated children in South Africa, the largest from a single country in Africa to date, were good with mortality of 7.7% and 81.1% of children alive and in care at 3 years. As expected, young age together with all markers of disease severity were independent predictors of mortality. These findings are strikingly similar to those of a similar combined cohort analysis of sub-Saharan paediatric ART programmes, the Kids' Antiretroviral Treatment in Lower-Incomes Countries (KIDS-ART-LINC) Collaboration.[8] Furthermore, follow-up monitoring of laboratory parameters was excellent, with more than 75% of children tested 6-monthly according to national guidelines. Although comparisons with rich countries are difficult owing to the older age of ART commencement in the South African children and inherent survival bias, the high level of virological suppression is encouraging and compares favourably with cohorts from Europe[20] and North America[21] and other African studies.[7,14] Similarly, children remaining in care experienced dramatic improvements in growth and immune status. While the proportion and absolute number of nearly 2 000 very young children accessing ART are much greater than in most other African studies, across the country older children are still preferentially accessing treatment with more than 70% of the cohort being over 18 months of age.[7,8,22]

Strengths and generalisablity of findings

This study is valuable because of the large number of children and length of follow-up, but particularly because of the high

Table III. Predictors of mortality using Cox-proportional hazards model stratified by site (adjusted for year of ART start)

Characteristic at ART start	Crude HR	95% CI	*p*-value	Adjusted HR Full model (*N*=2 449)	95% CI	*p*-value
WAZ			<0.001*			<0.001*
>–2	1			1		
–3 - –2	1.93	1.29 - 2.89		1.13	0.69 - 1.87	
< –3	5.23	3.84 - 7.12		2.44	1.65 - 3.59	
Viral load (copies/ml)			<0.001*			0.010*
<100 000	1			1		
100 000 to 1 million	1.75	1.24 - 2.45		1.68	1.02 - 2.76	
>1 million	3.30	2.32 - 4.70		2.22	1.31 - 3.77	
Severe immunosuppression (WHO definition)	4.23	2.55 - 7.00	<0.001	3.83	1.68 - 8.72	0.001
WHO stage 3 or 4 (v. 1 or 2)	3.01	2.00 - 4.54	<0.001	2.16	1.28 - 3.62	0.004
Age			<0.001*			0.002*
>3 yrs	1			1		
1 - 3 yrs	1.31	0.98 - 1.74		1.17	0.76 - 1.84	
<1 yr	3.38	2.65 - 4.31		2.00	1.30 - 3.07	
ART commenced before 2006	1.28	1.02 - 1.60	0.036	1.68	1.18 - 2.39	0.004

p-values derived from likelihood ratio tests.

absolute number of those under 18 months of age. With new WHO guidelines encouraging early ART initiation in infants, a better understanding of clinical outcomes in this age group is required.[3] In addition, the availability of regular viral load information is unusual in the African context. Inclusion of children from a number of different sites in 3 provinces and at different levels of care enhances representivity, while uniformity of treatment protocols lends itself to collation into a single analysis.

Limitations

Although the study includes some of the busiest routine public sector clinics, it should be acknowledged that IeDEA collaboration sites must have capacity for electronic collection of routine data, which is not the norm. Some high-burden provinces are not included in the study, and there is disproportionate representation of sites with tertiary care capacity. The thorough monitoring and high number of infants on ART therefore probably represent best-practice examples in well-resourced clinics.

While LFU in this study is relatively low compared with adult publications of routine cohort data,[23] there is variation in LFU at different sites. This is of concern as many of those who are LFU are likely to have died, resulting in under-ascertainment of mortality. Indeed, while there are various plausible explanations for the apparent protective effect on mortality of starting ART after 2005 (including that children starting earlier are 'sicker' in ways not captured by markers of disease severity available for this analysis), the contribution of increasing LFU in later years as programmes expand should not be underestimated. In this respect, the effect of choice of first drug (zidovudine v. stavudine) on mortality could not be definitively assessed owing to changes in prescribing patterns after the introduction of national treatment guidelines in 2004 and increasing LFU over time. The high transfer rate from tertiary sites to lower levels of care limits duration of follow-up for these patients. Systems of data collection integrated across sites are needed to ascertain outcomes for transferred patients.

Poor integration of health information systems is also reflected in the paucity of PMTCT exposure data. This reflects poor integration of antenatal, routine child care and HIV services themselves within the health system, a major barrier to timeous HIV diagnosis and referral for care of those infants infected despite PMTCT exposure.[7,22,24] Completeness and accuracy of other exposure variables is also limited, while historical changes in the WHO staging system limit its value as a measure of disease advancement.

Reflections on the South African national paediatric ART programme

This study indicates that the programme is successful *for those children who access it*. The latter caveat is important, as the fact that 20% of all children are treated at a handful of sites, all in large urban centres, suggests that considerable inequities in access are likely. Nevertheless the fastidious monitoring, utilisation of first-line regimens recommended in national guidelines, good survival, high proportions of children with viral suppression and favourable immune and growth responses – at least at these sites – are encouraging. The Western Cape has the specific aim of treating children at their nearest health centre whenever possible, with only those warranting specialist care remaining at tertiary facilities.[24]

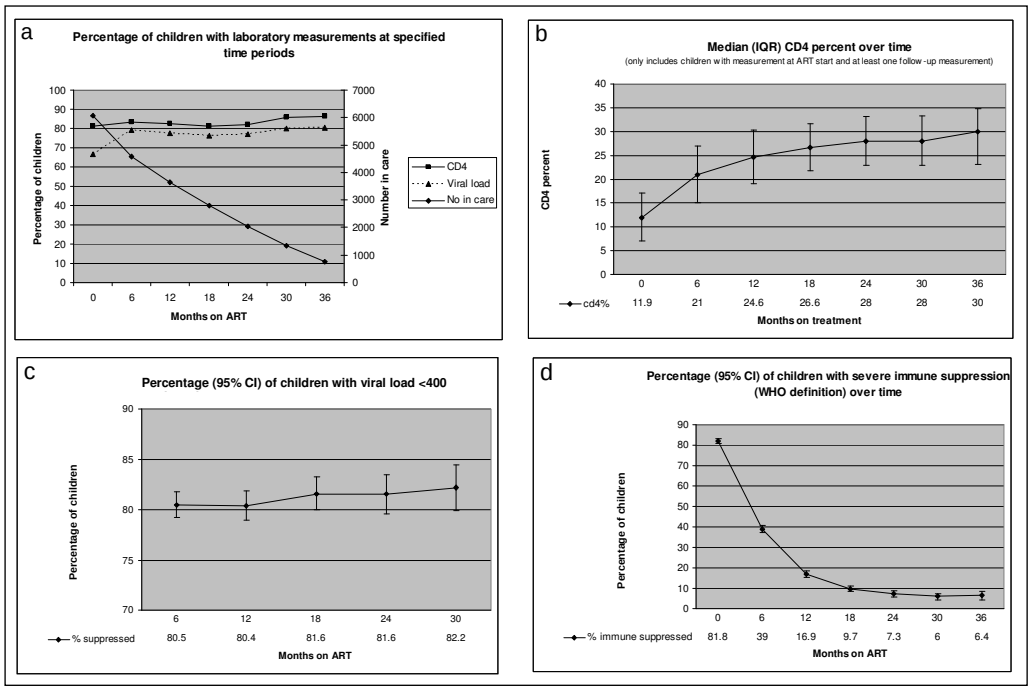
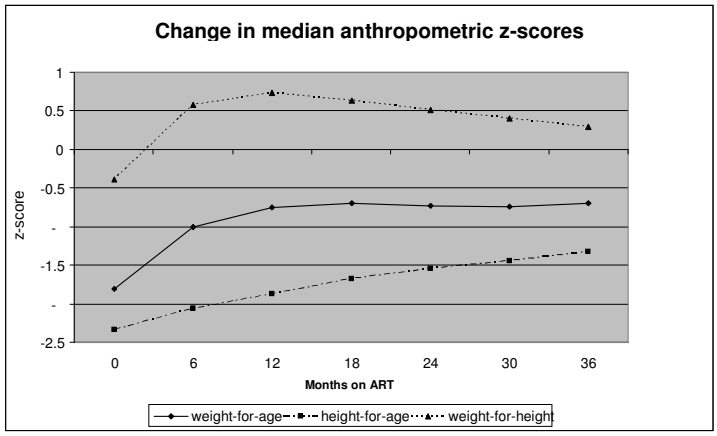


Fig. 2. Immune and virological response to ART.



Change in anthropometric z-scores during ART

Months on ART	0	6	12	18	24	30	36
No. in care <10 years of age*	5 535	4 009	3 063	2 357	1 739	1 185	653
Median weight-for-age	−1.81	−1.00	−0.75	−0.70	−0.73	−0.74	−0.69
IQR	−2.97 to −0.87	−1.75 to −0.20	−1.48 to 0.00	−1.43 to 0.00 1	−1.42 to −0.07	−1.39 to −0.10	−1.30 to −0.09
N	2 966	2 893	2 105	543	1 095	725	350
Median height-for-age	−2.34	−2.06	−1.87	−1.66	−1.54	−1.44	−1.32
IQR	−3.28 to −1.43	−2.89 to −1.20	−2.64 to −1.08	−2.42 to −0.92	−2.27 to −0.82	−2.13 to −0.76	−2.02 to −0.60
N	2 732	2 639	1 925	1 382	970	637	281
Median weight-for-height	−0.39	0.58	0.74	0.64	0.52	0.41	0.30
IQR	−1.53 to 0.60	−0.23 to 1.34	−0.06 to 1.47	−0.07 to 1.38 1	−0.08 to 1.26	−0.2 to 1.13	−0.34 to 1.06
N	2 355	2 281	1 623	134	780	488	202

*z-scores only calculated for children <10 years at time of measurement.
†Only includes children with measurement at ART start and at least one follow-up measurement.

Fig. 3. Growth response to ART (only includes children with measurement at ART start and at least one subsequent measurement).

In this respect, the rapid transfer of children from exclusive tertiary to primary care sites, together with the difference in ages of children starting ART at different levels of care, indicate that children are indeed receiving care at the appropriate level.

Although the cohort includes several infants, the number is negligible compared with the estimated 64 000 new infections that occur perinatally and through breastfeeding every year.[25] Together with lack of integration of antenatal PMTCT and paediatric HIV services, perceived and actual lack of expertise in the care of young HIV-infected infants pose significant barriers to access for infants, who are still largely cared for at tertiary sites. These problems need to be addressed urgently if South Africa seeks to implement revised WHO guidelines recommending early ART for infants irrespective of disease severity.[3]

In this respect it should be noted that the relatively poor outcomes for infants in this study would not necessarily be the scenario should infant ART initiation be prioritised. Disease progression is rapid in HIV-infected infants, and in this study children commencing ART at a young age are those whose disease progressed rapidly enough to meet previous WHO disease severity criteria while they were still young *and* who were able to access treatment before otherwise inevitable early death.[26] Better outcomes for older children represent a survivor effect, with older age at ART initiation being a proxy for slower disease progression. In contrast, other South African studies have shown excellent outcomes for infants commencing ART before disease progression.[27,28]

Conclusion

This study of a substantial proportion of the South African national ART programme for children demonstrates the dramatic

clinical benefit for those accessing the programme. The higher mortality in infants and young children and those with advanced disease highlights the need to identify HIV-infected infants and commence ART before disease progression.

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Conflict of interest. The authors declare that they have no conflict of interest.

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2.3 Prognosis of children with HIV-1 infection starting antiretroviral therapy in Southern Africa: a collaborative analysis of treatment programs

Paper overview

This paper analysed data from >12,000 children who initiated ART at IeDEA-SA sites to develop a prognostic model of one-year mortality for children initiating ART in the region. Weibull survival models were used to construct two prognostic models with and without CD4 measures respectively because these are not routinely measured in many programs. A method of internal-external cross-validation was used to identify the model of mortality that was most generalizable across the cohorts. Multiple imputation was used to account for missing data at ART start.

Contribution to the thesis and novelty

This paper addresses the second objective of the thesis, by examining the generalizability of survival outcomes and their associations across the Southern African region. Unique contributions include the development of the first generalizable prognostic model of mortality for children initiating ART in resource-limited settings. The model showed good discrimination and prognostic separation. It provides absolute predictions of mortality for up to one year on ART for children with particular age and disease severity characteristics. Development and comparison of models that included and excluded CD4% as a marker of disease severity suggested that low cost prognostic markers such as anaemia and WAZ score might be almost as good as CD4% for predicting mortality.

Role of the candidate

The candidate was responsible for all data management to generate the IeDEA paediatric data set for analysis. She was solely responsible for the analysis. A poster including this data was presented at the 4th International Workshop on HIV/Pediatrics in Washington in 2012. The candidate drafted the manuscript, incorporated input from co-authors and was responsible for finalising and submitting the final version of the manuscript for publication.

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TITLE: Prognosis of children with HIV-1 infection starting antiretroviral therapy in Southern Africa: a collaborative analysis of treatment programs

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ABSTRACT

Background: Prognostic models for children starting antiretroviral therapy (ART) in Africa are lacking. We developed models to estimate the probability of death during the first year on ART in Southern Africa.

Methods: We analyzed data from children ≤10 years old that started ART in Malawi, South Africa, Zambia or Zimbabwe from 2004-2010. Children lost to follow-up or transferred were excluded. The primary outcome was all-cause mortality in the first year of ART. We used Weibull survival models to construct two prognostic models: one with CD4%, age, WHO clinical stage, weight-for-age z-score (WAZ) and anemia and one without CD4%, because it is not routinely measured in many programs. We used multiple imputation to account for missing data.

Results: Among 12,655 children, 877 (6.9%) died in the first year of ART. 1780 children were lost to follow-up/transferred and excluded from main analyses; 10875 children were included. With the CD4% model probability of death at 1 year ranged from 1.8% (95% CI: 1.5–2.3) in children 5-10 years with CD4% ≥10%, WHO stage I/II, WAZ ≥-2 and without severe anemia to 46.3% (95% CI: 38.2–55.2) in children <1 year with CD4% <5%, stage III/IV, WAZ< -3 and severe anemia. The corresponding range for the model without CD4% was 2.2% (95% CI: 1.8–2.7) to 33.4% (95% CI: 28.2-39.3). Agreement between predicted and observed mortality was good.

Conclusion: These models may be useful to counsel children/caregivers, for programme planning and to assess programme outcomes after allowing for differences in patient disease severity characteristics.

Prognosis of children with HIV-1 infection starting antiretroviral therapy in Southern Africa: a collaborative analysis of treatment programs

INTRODUCTION

Despite the impressive increase in access to antiretroviral therapy (ART) for HIV-infected children in low-income settings, mortality is still high. In 2010, an estimated 230,000 children died of AIDS in sub-Saharan Africa.[1] While many deaths occur in untreated patients,[2] mortality remains high during the first year of ART, especially for children starting therapy with advanced disease.[3-5] Knowing the short term prognosis associated with particular disease severity characteristics is important for the individual child initiating ART and his/her caregiver, as well as for clinicians and for program planning. Further, comparison of actual mortality outcomes with predictions from a prognostic model that is generalizable across settings may be useful for benchmarking the quality of health care provision. Prognostic models for mortality on ART have to date been developed for adults in high and low-income settings,[6-8] but not for children.

The characteristics associated with mortality in children starting ART have been well described from a range of settings across sub-Saharan Africa.[3-5,9-13] However, the combined power of different markers of disease severity to predict mortality and the absolute mortality risk associated with these markers remains unknown. Young children and those with a low CD4% or advanced clinical disease are at particularly risk of high morbidity and mortality.[3,4,9,14] WHO Guidelines for ART eligibility are thus based on age, CD4 measures and disease stage.[15] Other variables also predict mortality and have been used to decide when to start ART: e.g. in high income countries in children >1 year old with minimal/no clinical symptoms HIV-1 RNA is used to determine ART eligibility[16] and HIV-1 RNA level and anemia have been shown to be independent risk factors for mortality.[9,11,17] In low income

settings, measurement of many of these prognostic factors, including CD4, is often unavailable due to lack of equipment, logistic constraints, personnel or high costs.[18]

The International epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) Collaboration includes data from children starting ART at 11 treatment programs in a range of settings in four countries.[3,14] We aimed to use these data to develop a prognostic model that estimates the cumulative probability of death at 3, 6 and 12 months after starting ART in children in Southern Africa according to age, and prognostic factors commonly measured in resource-limited settings. Separate models were developed for settings with and without access to CD4% at ART initiation.

METHODS

Treatment programs

IeDEA-SA is a regional collaboration of ART programs, which is part of a larger international network.[19] Data are collected at ART initiation and follow-up visits, using standardized instruments, and transferred at regular intervals to data centers at the Universities of Cape Town, South Africa, and Bern, Switzerland. All sites have ethical approval to collect data and participate in IeDEA-SA. The current analyses were based on data from 11 programs in four countries (Figure 1), including eight clinics in three provinces in South Africa (Red Cross Children's Hospital, Khayelitsha and Gugulethu ART Programs in Cape Town and Tygerberg Academic Hospital in Stellenbosch, Western Cape; Sinikithemba Clinic at McCord Hospital in Durban and Hlabisa HIV Treatment and Care Programme, Kwazulu-Natal; Harriet Shezi Children's Clinic at Chris Hani Baragwanath Hospital in Soweto and Rahima Moosa Mother and Child Hospital in Johannesburg, Gauteng) and one treatment program each in Zambia (Ministry of Health and Centre for Infectious Disease Research in Zambia program [MoH-

CIDRZ] in Lusaka), Malawi (Lighthouse Trust Clinic at Kamuzu Central Hospital in Lilongwe) and Zimbabwe (Newlands Clinic in Harare).

Inclusion criteria

All HIV-infected, ART-naïve (except for antiretroviral exposure to prevent vertical transmission) children who initiated treatment with ≥3 antiretrovirals at age ≤10 years between 1 January 2004 and 31 January 2010 were eligible. Children with <1 year of potential follow-up (ART initiation <1 year prior to site database closure) were excluded. Children were excluded from the main analysis if, within 6 months of starting ART, they were lost to follow-up (LTFU) or transferred out (TFO) to a different treatment site. As clinic visits may be up to 6 months apart, LTFU was defined as the last visit being ≥270 days before database closure.

Outcomes and prognostic models

We used an intention-to-continue-treatment analysis, ignoring treatment changes and interruptions. The outcome was all-cause mortality during the first year on ART. Follow-up was censored on the earliest of: date of death, last visit date +90 days in children LTFU/TFO, or 1 year after ART initiation. The 11 cohorts were grouped into five geographic regions as some cohorts had small patient numbers (Figure 1). Three regions were provinces within South Africa where ART programs at different sites are co-ordinated by provincial Departments of Health (Western Cape, Kwazulu-Natal and Gauteng). The fourth region comprised two cohorts with similar patient characteristics in Malawi and Zimbabwe, while the MoH-CIDRZ cohort (Zambia) comprised the 5th region.

The following prognostic variables measured at ART initiation were considered for inclusion in a prognostic model and associations with mortality were explored using Kaplan-Meier survival curves for each variable in the pre-specified categories of age (<1 year, 1 year, 2-4

years, 5-10 years); WHO Clinical Stage (I/II compared to III/IV); CD4% (<5, 5-9.9, 10-14.9; ≥15); anemia (defined as severe, moderate, mild/none using CDC classification of adverse events that incorporates both hemoglobin and age[20]); weight-for-age z-score (WAZ) calculated using WHO 2006 standards (<-3.00; -3.00 to -2.01, -2.00 to -1.01 and ≥-1.00 standard deviations below mean).[21] Apart from age and gender, data on prognostic variables were not recorded for all patients. Missing data were modeled using multiple imputation by chained equations using the ice command in STATA, with 25 imputed datasets.[22-24] The following variables were used in imputation equations: cohort, sex, age, WHO Stage, CD4%, WAZ, hemoglobin, interactions between age, CD4% and WAZ, as well as the outcome (death). Log or square root transformations were used for non-normally distributed variables. Weibull proportional hazards models were used to explore crude and adjusted associations between prognostic variables and mortality.

A set of candidate models (with and without CD4%) were selected using the Akaike Information Criterion (AIC) that penalizes model complexity. These were all flexible parametric survival models[25] with spline smoothing of the baseline hazard in order to model the steep mortality during the first 3 months of treatment. We used a system of leave-one-out cross-validation to select the most generalizable models with and without CD4%.[26,27] This method fits the model in four regions and tests discrimination of predictions of the fitted model when applied to the omitted fifth region. This is repeated sequentially rotating around the omitted region. Discrimination was assessed using the D-statistic (averaged across the imputed datasets) that measures the prognostic separation between the survival distributions for two independent prognostic groups.[27] We calculated the D-statistic for the model fitted on the four regions and applied to the excluded region (D_{test}) and compared this to the D-statistic for the model when co-efficients were re-estimated using data only from the excluded region (D_r). The difference (D_r-D_{test}) is a measure of the degradation in model fit and discrimination

when applied to independent data compared with when applied to the data that was used to estimate the model coefficients. Models with a low AIC score, high D_{test} and low D_r-D_{test} were favored.

Concordance between predicted mortality and observed mortality for the final selected models was assessed using Harrell's C-statistic (0.5 = agreement expected by chance; 1 = perfect agreement). The explained variation (R^2) of the final selected models was calculated.[28] Model calibration was assessed by comparing Kaplan-Meier curves of observed mortality with curves predicted from the model for groups with poor to good prognosis, and for each region. All analyses were conducted in STATA version 12.0 (STATA Corporation, College Station, Texas). Results are reported as Kaplan-Meier estimates or modeled estimates of mortality and crude and adjusted hazard ratios (HR), with 95% confidence intervals (CI).

Sensitivity analyses

In sensitivity analyses we included children LTFU/TFO within the first six months of treatment. We examined Kaplan-Meier estimates of one-year mortality first censoring their follow-up time at the last visit date +90 days, and then assuming 30% and 50% mortality in those LTFU/TFO with time to death randomly assigned based on the distribution in those not LTFU/TFO. Finally, we developed models including children LTFU/TFO, censoring their follow-up time at the last visit date +90 days.

RESULTS

A total of 12,655 children started ART in the 11 treatment programs. 1780 children (14%) were lost to follow-up or transferred and excluded from the main analyses. The main analysis included 10,875 children (70% ≥2 years old) with 10,204 child-years of follow-up (Table 1). Most children had advanced disease at ART initiation (72% WHO Clinical Stage III/IV;

median [IQR] CD4%: 13% [8-19]). There was considerable between-region heterogeneity in age and disease severity; the percentage of children <1 year old ranged from 3% to nearly 30%; the percentage with WHO Stage III/IV disease ranged from approximately 60% to >90%. There was also substantial missing data on many covariates; anemia and CD4% were not reported for 37% (range across regions:18-88%) and 32% (16-56%) of children respectively. The estimated cumulative mortality by 1 year after ART start was 8.6% (95% CI: 8.0-9.2) (range across regions: 5.8%-10.5%).

The Kaplan-Meier curves of death for the different prognostic characteristics are shown in Figure 2. Mortality was highest in the first three months on ART especially for those with the worst prognosis. Age was strongly associated with mortality, with much higher mortality in those <2 years compared to older children. The other prognostic variables were therefore examined separately for these two age groups. Advanced disease stage, lower CD4% and WAZ and more severe anemia were all associated with mortality. While CD4% and WAZ had a graded association with mortality across all categories in younger children, in those >2 years old there was a large impact of an increase in CD4% from <5 to 5-9.9% and WAZ from <-3 to -3 to -2 with smaller reductions in mortality associated with further increases.

The associations between prognostic variables and mortality are shown in Table 2 (using multiple imputation to account for missing data) and Appendix Table S1 (using available data only). In mutually adjusted analyses there were associations between all disease severity characteristics and mortality, however the association between HIV-1 RNA and mortality was substantially attenuated by adjustment. Since HIV-1 RNA was missing for most children from outside South Africa, it was excluded from further analyses. In both available data and imputed data there was a significant interaction between age and both CD4% (p=0.007 [available data]; p=0.028 [imputed data]) and WAZ (p<0.001 [available data]; p=0.002 [imputed data]). The effect of an increase in either of these variables had a greater impact on

reducing mortality risk in older children compared to younger children (appendix Table S2), although mortality overall was lower for older children.

The two final models selected by internal-external cross-validation included age (in four categories), clinical stage (two), WAZ (three) and anemia (two), with one model additionally including CD4% (in three categories, Table 3). There were thus 144 risk groups (model with CD4%) or 48 risk groups (model without CD4%). The C-statistics over the entire first year on ART were 0.753 and 0.745 for the models with and without CD4% respectively. Concordance was lower when restricting to the second six months on ART (C-statistics of 0.708 and 0.705 for models with and without CD4% respectively). The R^2 values were 32.1% and 31.1% for the whole first year and 23.6% and 23.9% for the second six months for the models with and without CD4% respectively.

For both models, predicted mortality closely followed actual mortality for five prognostic groups of children with approximately 20% of deaths in each group (Figure 3[a]). The majority of children (57% [model with CD4%] and 58% [model without CD4%] were in the group with a good prognosis and one-year mortality <5%. Predicted mortality from the model with CD4% closely approximated actual mortality for all regions except Kwazulu-Natal (observed>predicted) and Malawi & Zimbabwe (observed<predicted) (Figure 3[b]). Predicted mortality from the model without CD4% only approximated observed mortality closely for CIDRZ (figure 3[b]). This was the only region where <20% of hemoglobin values were missing. In other regions, hemoglobin may not have been well imputed, particularly in Gauteng and Malawi & Zimbabwe where >60% of values were missing.

Children aged <1 year in clinical stage III/IV with WAZ <-3, severe anemia and CD4% <5 had the highest predicted cumulative mortality at one year (46.3%) and children aged 5-10 years in stage I/II with WAZ ≥-2, no severe anemia and CD4% ≥ 10 the lowest mortality (1.8%). The corresponding estimates from the model without CD4% were 33.4% and 2.2%.

Predictions for all possible combinations of prognostic variables are shown in appendix Table S3. A risk calculator based on the prognostic models is available at the collaboration's website (www.iedea-sa.org).

The 1780 children LTFU/TFO within the first six months of treatment were younger and had more advanced disease compared to those included (appendix Table S3). When including these children in sensitivity analyses, Kaplan-Meier one-year mortality estimates ranged from 7.2% (censoring children LTFU/TFO at last visit date +90 days) to 11.6% and 14.4% (assuming 30% and 50% mortality in those LTFU/TFO respectively). When developing the prognostic models including all children (censoring children LTFU/TFO as above) the predicted cumulative one-year mortality ranged from 1.72% to 39.0% (CD4% model) and from 2.1% to 27.7% (model without CD4%).

DISCUSSION

Main findings

These prognostic models that predict one year mortality in HIV-infected children on ART are generalizable and show good discrimination and prognostic separation. These models demonstrate that the majority of children (>55%) starting ART and remaining in care have a one year mortality risk of ≤3%, with 6% of children having >20% predicted risk of dying within the first year on ART. For predicting mortality on ART, low cost prognostic markers such as WAZ and anemia may be almost as good as CD4%. In busy scale-up programs without access to CD4%, this may allow for risk-stratification of children initiating ART.

Overall mortality, loss to follow-up and transfer out

There was substantial heterogeneity between regions both in overall mortality rate and disease characteristics and age. Crude mortality was highest in the Western Cape province where the

only treatment sites providing exclusively tertiary care were located and which has the highest proportion of children <2 years old initiating treatment. These sites also rapidly transfer children to primary care once they are getting better (12.7% TFO from Western Cape exclusively tertiary care sites between six and twelve months on ART)[29] which may result in an over-estimate of overall mortality. We excluded children who were LTFU/TFO within six months of starting ART to reduce bias by underascertainment of deaths if these patients had been censored, and more closely reflect the situation of children remaining in care. This does not completely remove bias as children classified as LTFU may have died before meeting the LTFU definition and mortality might be higher in children LTFU compared to children remaining in care.[8] Tracing studies have demonstrated that a substantial proportion of children LTFU may have died.[30,31] For example, in Malawi 33% of children traced after being LTFU had died[31]. Our sensitivity analysis including children LTFU/TFO in the first six months of ART showed that assumptions about their mortality impact on estimated overall mortality, and their exclusion may result in underestimated predicted mortality at the program level. Indeed, excluded children were more likely to have characteristics associated with mortality compared to those included in the main analysis.

Comparison to pre-ART prognostic model

While this is the first prognostic model for children on ART, a similar model for pre-ART mortality has been developed in children from high income settings.[32] A weighting system incorporating weight percentile, WHO stage, symptoms, general health rating, total lymphocyte count, packed cell volume and albumin predicted mortality well with a C-statistic of 0.852 (higher than the values of 0.753 and 0.745 for our models with and without CD4% respectively). The study also showed that CD4% can be replaced by simpler measures to predict pre-ART mortality. However, as expected from high income settings, children had less

advanced disease. Furthermore, the mothers of all children participated in a randomized trial and the model may not be applicable to routine care in resource-limited settings.

Comparison with adult model

Our pediatric model compares favorably with the adult model for resource-limited settings (higher R^2 and C-statistic) although the range of predictions and the number of strata is more limited.[8] This is probably due to the powerful prognostic value of age in children. Mortality declines rapidly with increasing age in all children, irrespective of HIV-infection. In the context of ART eligibility in a peri-natally HIV-infected child only after "waiting" for certain disease severity criteria to be met, the age at which a child starts therapy is a proxy for rate of disease progression since birth and thus a strong prognostic factor.[3] The model predictions would therefore not be applicable to children <2 years old who start ART before clinical/immunological progression as recommended in the WHO 2010 guidelines.[15] These guidelines are based on the Children with HIV Early Antiretroviral Therapy (CHER) trial which demonstrated a favorable prognosis in children <1 year old starting ART before disease progression.[33]

Strengths and limitations

To our knowledge this is the first pediatric prognostic model of mortality on ART and is based on a very large cohort across a range of settings. The large number of missing values for some variables (e.g. hemoglobin) is a limitation but reflects the reality of many ART programs in the region. In particular, this limited our ability to determine whether a model based on hemoglobin alone was as good as including both CD4% and hemoglobin for prognostic purposes. Due to imputation of a large proportion of hemoglobin values for all regions except Zambia, there was misfit of predicted mortality at the level of the region for the model without CD4% (Figure 3[b]). However, there was very little difference in measures of fit when restricting to patients in whom hemoglobin was measured, and the fit of the

models with and without CD4% were comparable in Zambia for which <20% of hemoglobin values were imputed. In addition, associations with mortality were similar if missing values were imputed or a complete case analysis was performed. This, together with the cross validation, underlines the robustness of our findings.

The majority of children in this analysis started ART with advanced disease, hence we were unable to examine mortality for higher values of CD4% and WAZ. This would have been particularly useful in children <2 years old where mortality predicted by this model is high even in those with the best prognostic markers. Nevertheless, the model predictions are applicable to most children starting ART as, even after introduction of the WHO 2010 guidelines, the majority of children in this region still commence ART with advanced disease.[34](Davies, personal communication)

Despite the fact that many sites from different settings are represented, the analysis was dominated by one large cohort in Zambia where the fit of predicted and observed mortality is best. Discrepancies between predicted and observed mortality for other regions may be due to differences in LTFU and mortality ascertainment, proportion of imputed data, differences in prognostic variables not measured or included in the models or differences in background mortality, access to health services and models of care. Other factors including nutrition supplements, co-trimoxazole prophylaxis, co-infections, choice of first-line ART, adherence, HIV-1 RNA and exposure to vertical transmission prevention regimens have been shown to be associated with outcomes in children.[11,35-38] However, these factors are often not easily available or recorded in low-income settings, and were indeed not available for many children in this analysis. There is a trade-off between models which would be more accurate but less applicable and useful in general health care settings in low-income countries. We did not consider treatment interruptions and did not adjust for possible temporal improvements in patient management. In addition all children came from largely urban regions and all sites

must have medical record systems available, so generalizability to less well-resourced cohorts may be limited.

In conclusion, this model demonstrates that the majority of children starting ART in Southern Africa have a low risk of one-year mortality, despite many having characteristics of severe disease. As more children are diagnosed and initiate ART early and the duration of follow-up increases, it is important to continue to monitor ART outcomes and develop prognostic models for long-term prognosis in children starting ART in infancy before developing severe disease.

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Figure 1: Location of the 11 treatment programs included in the analysis and their grouping into 5 regions.

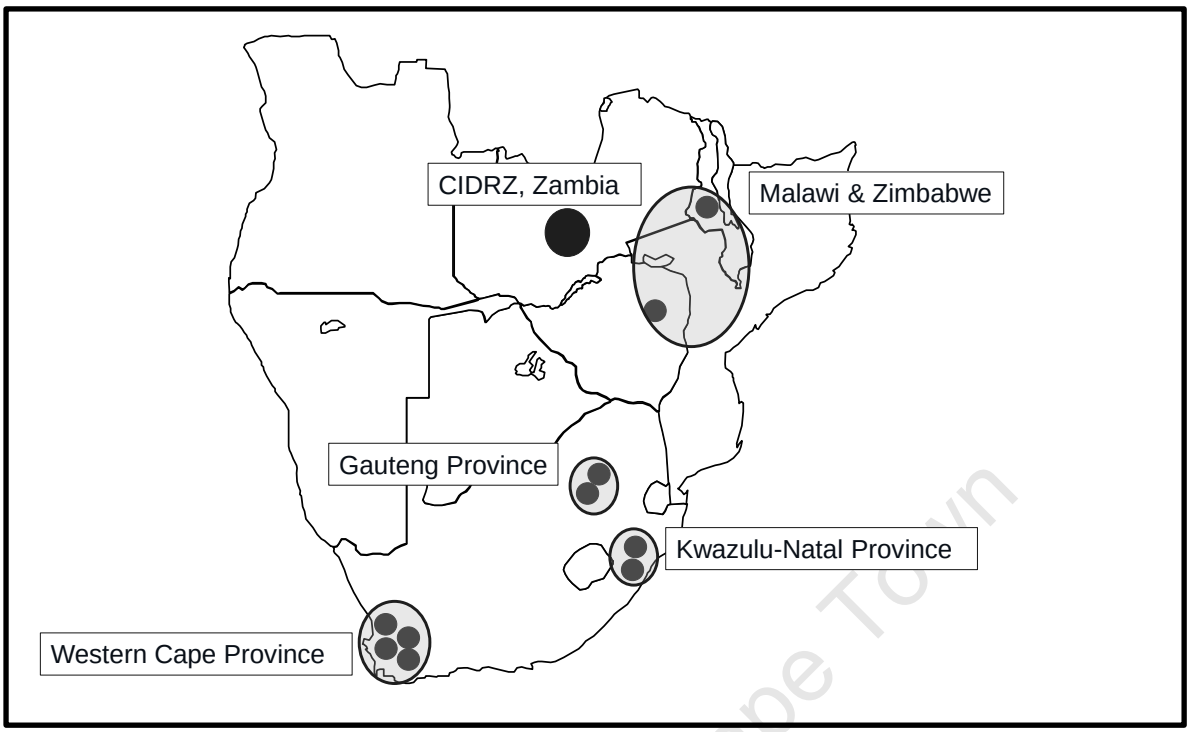


Table 1: Pediatric ART programs with number of patients, characteristics at ART initiation, follow-up duration, status by 1 year after ART initiation and Kaplan-Meier estimates of mortality by 1 year after ART initiation.

Region	Western Cape	Gauteng	Kwazulu-Natal	Malawi & Zimbabwe	Zambia	Total
Number of children	1505 (14%)	2015 (19%)	791 (7%)	706 (6%)	5858 (54%)	**10875**
Sex						
Female	720 (48%)	997 (49%)	396 (50%)	364 (52%)	2883 (49%)	**5360 (49%)**
Male	785 (52%)	1018 (51%)	395 (50%)	342 (48%)	2975 (51%)	**5515 (51%)**
Age group						
< 1 year	441 (29%)	306 (15%)	74 (9%)	23 (3%)	583 (10%)	**1427 (13%)**
1 year	290 (19%)	282 (14%)	128 (16%)	71 (10%)	1008 (17%)	**1779 (16%)**
2-4 years	412 (27%)	629 (31%)	224 (28%)	219 (31%)	1809 (30%)	**3293 (30%)**
5-10 years	362 (24%)	798 (40%)	365 (46%)	393 (56%)	2458 (40%)	**4376 (40%)**
WHO Stage						
I/II	241 (18%)	461 (41%)	98 (19%)	37 (6%)	1746 (31%)	**2583 (28%)**
III/IV	1078 (82%)	669 (59%)	428 (81%)	538 (94%)	3964 (69%)	**6677 (72%)**
Not reported	186 (12%)	885 (44%)	265 (34%)	131 (18%)	148 (3%)	**1615 (15%)**
Anaemia						
Mild/none	903 (83%)	209 (87%)	464 (85%)	196 (87%)	3736 (78%)	**5508 (80%)**
Moderate	114 (10%)	18 (8%)	54 (10%)	18 (8%)	590 (12%)	**794 (12%)**
Severe	72 (7%)	13 (5%)	31 (6%)	11 (5%)	461 (10%)	**588 (9%)**
Not reported	416 (28%)	1775 (88%)	242 (31%)	481 (68%)	1071 (18%)	**3985 (37%)**
Median (IQR) CD4%	13 (9 to 19)%	11 (7 to 15)%	13 (8 to 17)%	14 (9 to 20)%	14 (9 to 20)%	**13 (8 to 19)%**
Not reported	460 (31%)	313 (16%)	230 (29%)	397 (56%)	2080 (36%)	**3480 (32%)**
Median (IQR) WAZ	-1.9 (-3.5 to -0.8)	-2.0 (-3.1 to -1.1)	-1.4 (-2.5 to -0.5)	-1.8 (-2.9 to -0.8)	-2.2 (-3.3 to -1.1)	**-2.0 (-3.2 to -1.0)**
Not reported	537 (36%)	385 (19%)	168 (21%)	213 (30%)	319 (5%)	**1622 (15%)**
Median (IQR) log_{10}HIV-RNA (copies/ml)	5.56 (4.97 to 6.09)	5.23 (4.69 to 5.79)	4.52 (3.81 to 5.26)	5.09 (4.62 to 5.45)		**5.27 (4.69 to 5.84)**
Not reported	430 (29%)	516 (26%)	459 (58%)	578 (82%)	5856 (>99%)	**7839 (72%)**
Follow-up (child years)	1377.9	1920.5	754	671.7	5480.2	**10204.3**
AT 1 YEAR[1]						
% in follow-up	86.4	92.3	92.0	89.7	87.3	**88.6**
% transferred	3.3	0.8	0.3	2.5	0	**0.8**
% LTFU	0.7	1.1	1.3	2.3	3.7	**2.5**
% deceased	9.6	5.8	6.4	5.5	9.0	**8.1**
1-year mortality rate						
K-M estimate (95% CI)	10.5 (8.9 to 12.4)	6.0 (5.0 to 7.2)	6.8 (5.1 to 8.9)	5.8 (4.2 to 7.9)	9.6 (8.8 to 10.5)	8.6 (8.0 to 9.2)

[1]Note that LTFU and transferred outcomes refer to children LTFU or transferred between 6 and 12 months after ART start as children LTFU/TFO within 6 months of ART start were excluded from the main analysis.

Figure 2: Kaplan-Meier curves of probability of death according to age in years

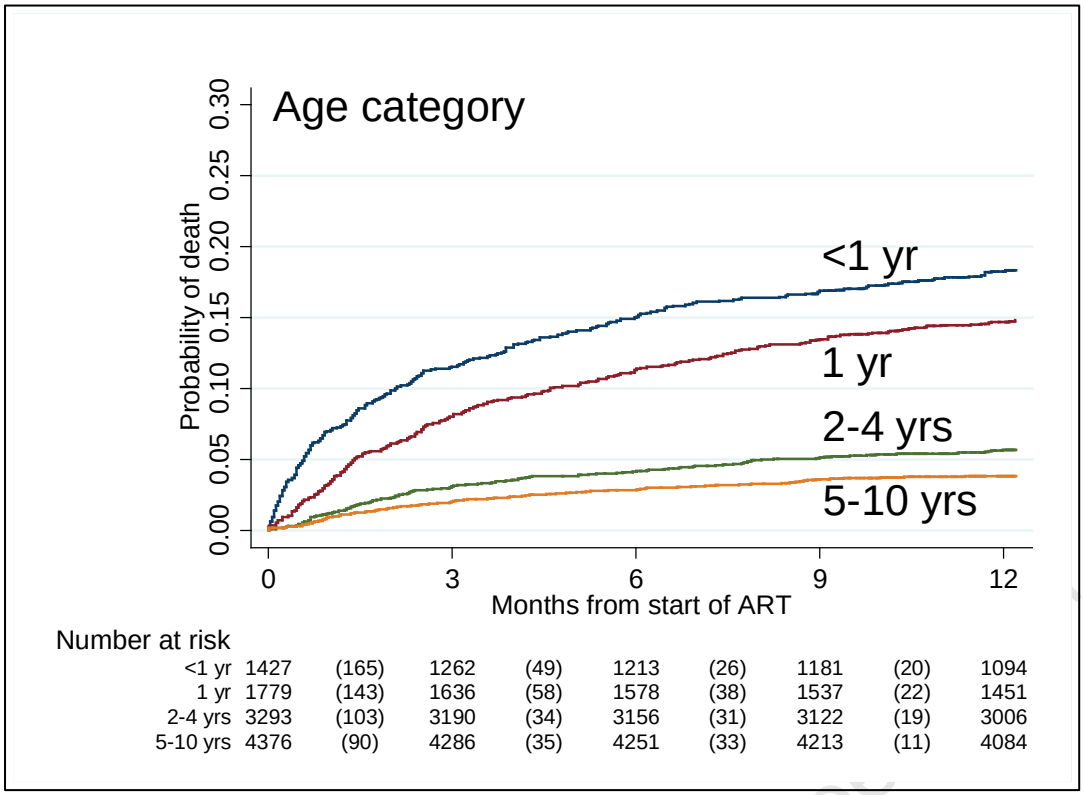


Figure 3: Kaplan-Meier curves of probability of death according to WHO Clinical Stage, CD4%, weight-for-age z-score and anemia for children <2 years of age (left panel) and 2-10 years of age (right panel).

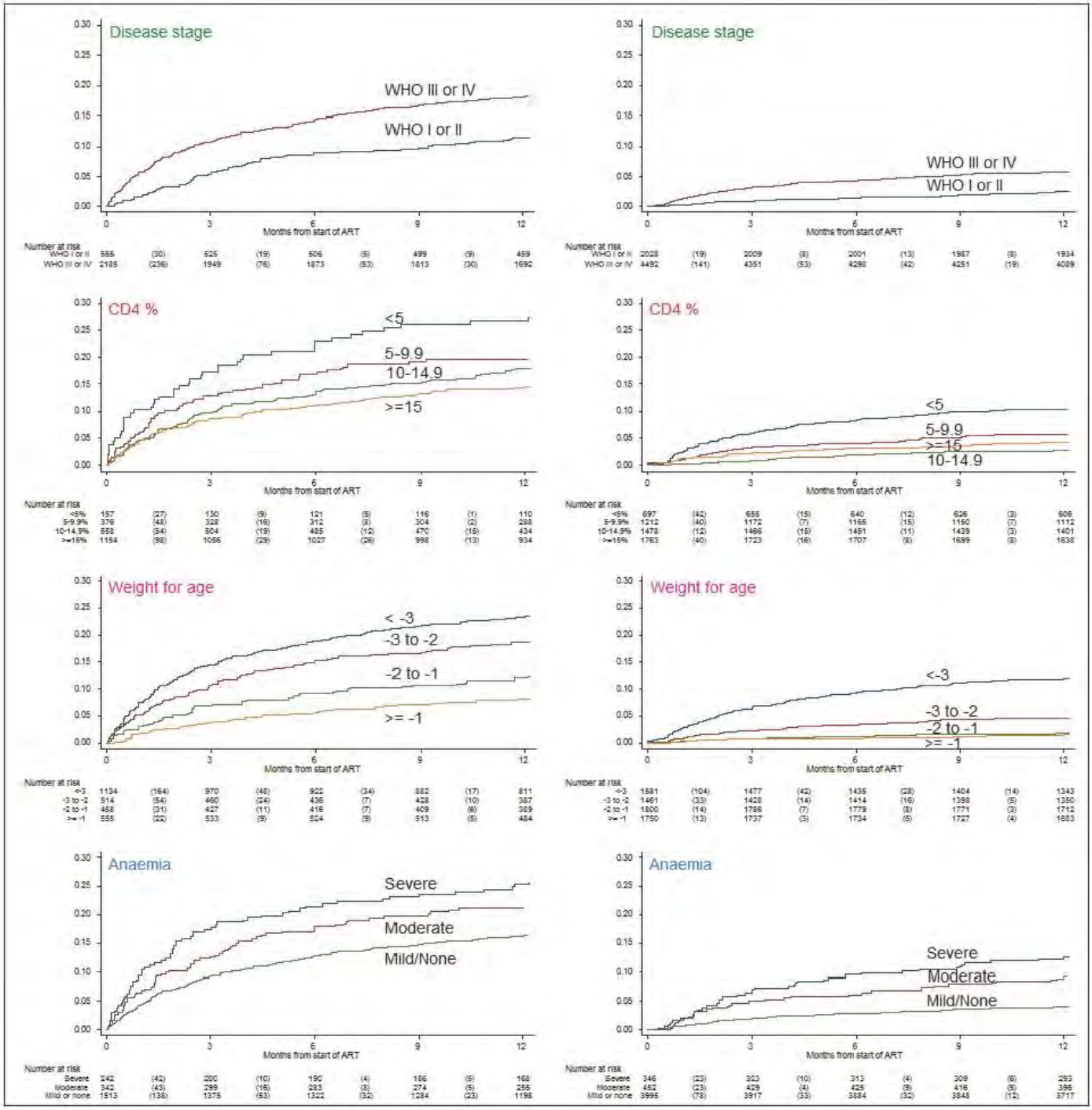


Table 2: Prognostic variables and mortality for children starting ART and not LTFU or TFO during the first 6 months of treatment in 11 treatment programs in Southern Africa.

					Analysis based on imputed data (25 multiple imputation datasets)	
Variable	Available data	N(%) missing	Person years	N deaths	Crude mortality HR n=10875	Adjusted mortality HR n=10875
Age (years)				877		
< 1	1427		1221	260	1	1
1	1779		1588	261	0.74 (0.62 to 0.88)	0.72 (0.39 to 1.33)[1]
2-4	3293		3152	187	0.27 (0.23 to 0.33)	0.31 (0.17 to 0.57)[1]
5-10	4376		4243	169	0.18 (0.15 to 0.22)	0.28 (0.17 to 0.46)[1]
Sex						
Male	5515		5178	438	1	1
Female	5360		5026	439	1.04 (0.91 to 1.18)	1.06 (0.93 to 1.21)
Stage		1615 (15)				
Less advanced	2583		2503	111	1	1
Advanced	6677		6179	650	2.21 (1.80 to 2.71)	1.93 (1.58 to 2.37)
CD4 percent		3480 (32)				
less than 5	854		766	114	1	1
5 to 9	1588		1479	143	0.72 (0.57 to 0.91)	0.84 (0.51 to 1.38)[2]
10 to 14	2036		1936	141	0.59 (0.47 to 0.75)	0.57 (0.34 to 0.96)[2]
≥ 15	2917		2733	238	0.64 (0.52 to 0.79)	0.59 (0.38 to 0.92)[2]
Anaemia		3985 (36)				
Severe	588		509	104	1	1
Moderate	794		710	113	0.80 (0.62 to 1.03)	0.83 (0.64 to 1.08)
Mild/none	5508		5206	401	0.43 (0.35 to 0.53)	0.61 (0.49 to 0.75)
Weight-for-age z-score		1622 (15)				
≤ - 3	2715		2373	451	1	1
-3 to -2	1975		1852	163	0.51 (0.43 to 0.61)	0.90 (0.62 to 1.29)[3]
-2 to -1	2258		2191	87	0.27 (0.21 to 0.33)	0.83 (0.57 to 1.21)[3]
≥ -1	2305		2251	70	0.21 (0.17 to 0.27)	0.52 (0.35 to 0.80)[3]

[1] HRs are shown for a child with CD4 percent <5%; [2] HRs are shown for a child < 1 year of age; [3] HRs are shown for a child <1 year of age with CD4 percent <5%

Table 3: Adjusted HRs for death in the selected best models with CD4% and withoutCD4%

	Model with CD4%	Model without CD4%
Variable	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**
Age		
<1 year	1	1
1 year	0.78 (0.66 to 0.93)	0.78 (0.66 to 0.93)
2 to 4 years	0.34 (0.28 to 0.41)	0.35 (0.29 to 0.43)
5 to 10 years	0.22 (0.18 to 0.27)	0.25 (0.2 to 0.3)
WHO Clinical Stage		
I or II	1	1
III or IV	1.39 (1.13 to 1.71)	1.39 (1.13 to 1.72)
CD4%		
<5%	1	not in model
5-9.9%	0.69 (0.54 to 0.87)	not in model
≥10%	0.56 (0.45 to 0.68)	not in model
Weight-for-age z-score		
<-3	1	1
-3 to -2	0.66 (0.55 to 0.79)	0.63 (0.53 to 0.76)
≥ -2	0.35 (0.29 to 0.42)	0.33 (0.27 to 0.4)
Anemia		
Severe	1	1
Mild/moderate/none	0.71 (0.57 to 0.88)	0.7 (0.57 to 0.87)

Figure 4 (a): Cumulative mortality predicted from prognostic models (dashed coloured lines) compared with Kaplan-Meier observed mortality (solid black lines) for five prognostic groups of children commencing ART, ranging from worst to best prognosis. Each group contains approximately 20% of deaths. Number of patients (%) is shown.

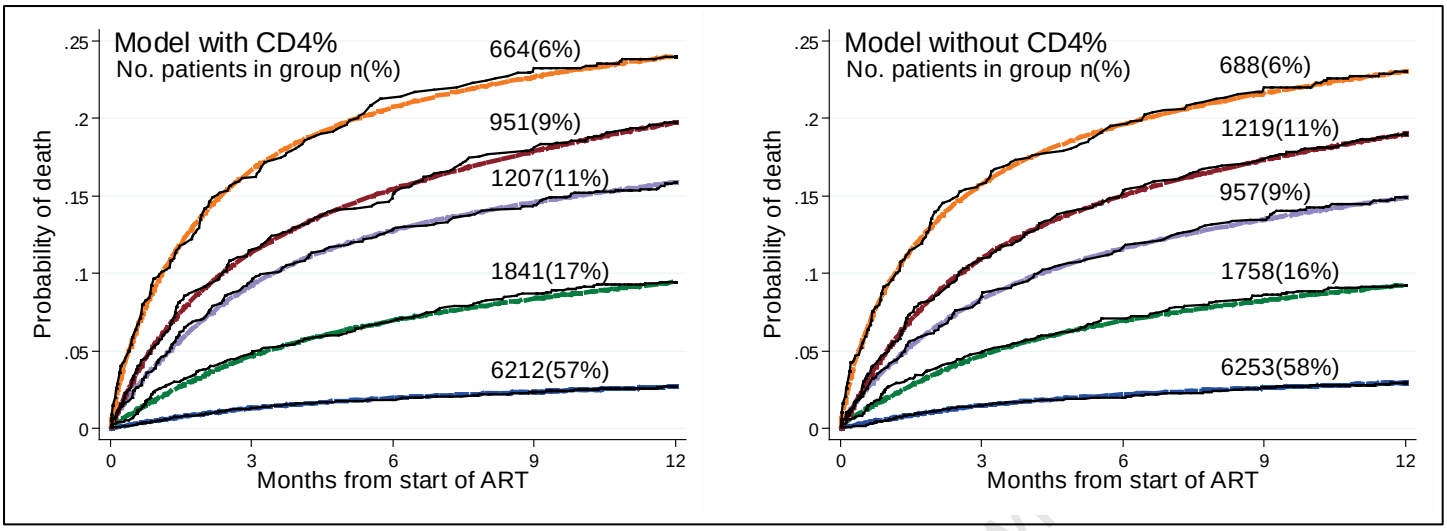
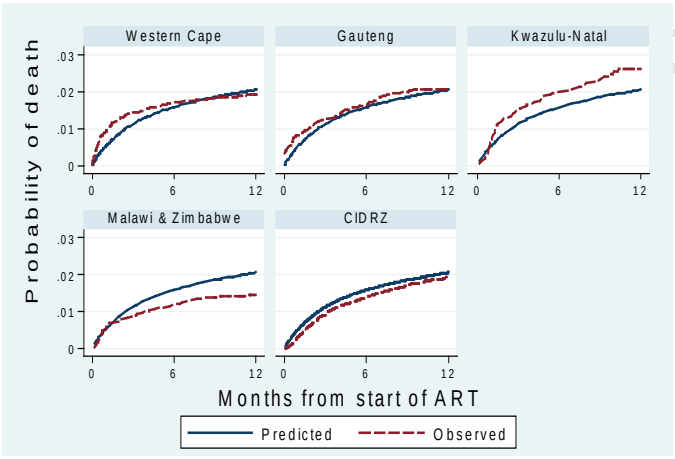
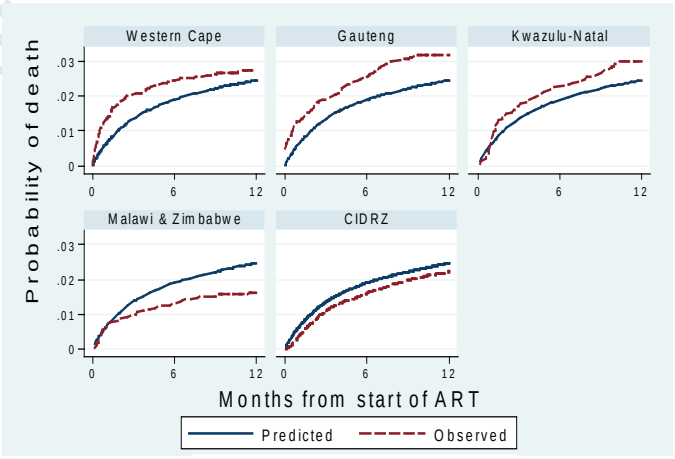


Figure 4 (b): Cumulative mortality predicted from prognostic models (dashed red lines) compared with Kaplan-Meier observed mortality for each region for patients with the most commonly occurring values of prognostic variables. Patients were aged 5-10 years with WHO Stage III/IV disease, CD4≥10% and WAZ -3 to -2.



Model with CD4%



Model without CD4%

Supplementary Tables

Table S1: Prognostic variables and mortality for children starting ART and not LTFU or TFO during the first 6 months of treatment in 11 treatment programs in Southern Africa – analysis of available data only.

					Analysis based on available data		
Variable	Available data	N(%) missing	Person years	N deaths	Crude mortality HR[1]	Crude mortality HR[2]	Adjusted mortality HR[2]
Age (years)				877	n=9259	n=6428	n=6428
< 1	1427		1221	260	1	1	1
1	1779		1588	261	0.73 (0.61 to 0.88)	0.66 (0.53 to 0.82)	0.59 (0.30 to 1.19)[3]
2-4	3293		3152	187	0.28 (0.23 to 0.34)	0.28 (0.22 to 0.35)	0.29 (0.16 to 0.56)[3]
5-10	4376		4243	169	0.16 (0.13 to 0.20)	0.16 (0.12 to 0.2)	0.23 (0.13 to 0.39)[3]
Sex					n=9259	n=6428	n=6428
Male	5515		5178	438	1	1	1
Female	5360		5026	439	0.97 (0.84 to 1.12)	0.99 (0.84 to 1.17)	1.04 (0.88 to 1.23)
Stage		1615 (15)			n=9259	n=6428	n=6428
Less advanced	2583		2503	111	1	1	1
Advanced	6677		6179	650	2.39 (1.95 to 2.93)	2.65 (2.09 to 3.37)	2.38 (1.87 to 3.03)
CD4 percent		3480 (32)			n=6428	n=6428	n=6428
less than 5	854		766	114	1	1	1
5 to 9	1588		1479	143	0.72 (0.55 to 0.94)	0.72 (0.55 to 0.94)	0.88 (0.51 to 1.51)[4]
10 to 14	2036		1936	141	0.54 (0.41 to 0.71)	0.54 (0.41 to 0.71)	0.49 (0.28 to 0.84)[4]
≥ 15	2917		2733	238	0.57 (0.45 to 0.74)	0.57 (0.45 to 0.74)	0.49 (0.30 to 0.79)[4]
Plasma HIV-RNA		7839 (72)			n=1852[6]	n=1706[6]	n=1706[6]
<5 log 10	1127		797	31	1	1	1
5 - 5.99 log 10	1337		1051	80	2.40 (1.45 to 3.96)	2.58 (1.51 to 4.42)	1.73 (1.00 to 3.00)
≥ 6 log	572		486	81	4.72 (2.85 to 7.79)	5.10 (2.98 to 8.73)	1.98 (1.12 to 3.51)
Anaemia		3985 (36)			n=6307	n=4888	n=4888
Severe	588		509	104	1	1	1
Moderate	794		710	113	0.76 (0.58 to 1.00)	0.71 (0.52 to 0.96)	0.71 (0.52 to 0.97)
Mild/none	5508		5206	401	0.37 (0.30 to 0.47)	0.38 (0.29 to 0.48)	0.51 (0.40 to 0.66)
Weight-for-age z-score		1622 (15)			n=8342	n=6120	n=6120
≤ - 3	2715		2373	451	1	1	1
-3 to -2	1975		1852	163	0.49 (0.41 to 0.59)	0.48 (0.39 to 0.60)	1.10 (0.74 to 1.65)[5]
-2 to -1	2258		2191	87	0.22 (0.17 to 0.28)	0.22 (0.17 to 0.29)	1.05 (0.68 to 1.61)[5]
≥ -1	2305		2251	70	0.17 (0.13 to 0.22)	0.16 (0.12 to 0.22)	0.45 (0.27 to 0.74)[5]

[1] Only includes patients with complete data on age, sex and stage; [2] Limited to children with complete date on age, sex, stage, CD4% and adjusted for these in adjusted analyses; [3] HRs are shown for a child with CD4 percent <5%; [4] HRs are shown for a child age <1 year; [5] HRs are shown for a child <1 year of age with CD4 percent <5%; [6] Limited to sites with plasma HIV-RNA recorded for at least 40% of children

Table S2: Hazard ratios for the associations between age, CD4% and WAZ adjusted for these variables as well as WHO Clinical Stage and sex, taking into account the interactions between age and CD4% and age and WAZ for (a) complete case data (N=6,428) and (b) data with missing covariate values modeled using multiple imputation (N=10,875)

(a)

AGE	WAZ	CD4% <5	CD4% 5-9.9	CD4% 10-14.9	CD4% ≥ 15
< 1 year	**< -3**	1	0.68 (0.38 to 1.21)	0.47 (0.27 to 0.82)	0.45 (0.27 to 0.74)
	-3 to -2	1.1 (0.74 to 1.65)	0.75 (0.38 to 1.49)	0.52 (0.27 to 1)	0.49 (0.27 to 0.9)
	-2 to -1	1.05 (0.68 to 1.61)	0.71 (0.36 to 1.41)	0.49 (0.25 to 0.96)	0.47 (0.25 to 0.87)
	≥ -1	0.45 (0.28 to 0.74)	0.31 (0.15 to 0.65)	0.21 (0.1 to 0.44)	0.2 (0.1 to 0.4)
1 year	**< -3**	0.69 (0.34 to 1.42)	0.44 (0.24 to 0.8)	0.61 (0.35 to 1.05)	0.3 (0.17 to 0.53)
	-3 to -2	0.53 (0.24 to 1.16)	0.33 (0.17 to 0.64)	0.46 (0.25 to 0.86)	0.23 (0.12 to 0.42)
	-2 to -1	0.22 (0.09 to 0.53)	0.14 (0.06 to 0.3)	0.19 (0.09 to 0.41)	0.1 (0.04 to 0.2)
	≥ -1	0.12 (0.05 to 0.32)	0.08 (0.03 to 0.19)	0.11 (0.05 to 0.25)	0.05 (0.02 to 0.12)
2-4 years	**< -3**	0.44 (0.22 to 0.85)	0.38 (0.21 to 0.68)	0.22 (0.12 to 0.42)	0.26 (0.15 to 0.47)
	-3 to -2	0.14 (0.06 to 0.3)	0.12 (0.06 to 0.24)	0.07 (0.03 to 0.15)	0.08 (0.04 to 0.17)
	-2 to -1	0.04 (0.02 to 0.12)	0.04 (0.02 to 0.1)	0.02 (0.01 to 0.06)	0.03 (0.01 to 0.07)
	≥ -1	0.09 (0.04 to 0.2)	0.08 (0.04 to 0.16)	0.04 (0.02 to 0.1)	0.05 (0.03 to 0.11)
5-9 years	**< -3**	0.3 (0.17 to 0.55)	0.15 (0.08 to 0.3)	0.1 (0.05 to 0.21)	0.1 (0.05 to 0.21)
	-3 to -2	0.16 (0.08 to 0.31)	0.08 (0.04 to 0.17)	0.05 (0.02 to 0.12)	0.05 (0.03 to 0.11)
	-2 to -1	0.07 (0.03 to 0.16)	0.04 (0.02 to 0.08)	0.02 (0.01 to 0.06)	0.02 (0.01 to 0.06)
	≥ -1	0.03 (0.01 to 0.1)	0.02 (0 to 0.05)	0.01 (0 to 0.03)	0.01 (0 to 0.03)

Table S2 (b)

AGE	WAZ	CD4% <5	CD4% 5-9.9	CD4% 10-14.9	CD4% ≥ 15
< 1 year	**< -3**	1	0.87 (0.52 to 1.44)	0.60 (0.36 to 1.00)	0.62 (0.40 to 0.98)
	-3 to -2	0.90 (0.62 to 1.29)	0.78 (0.41 to 1.45)	0.54 (0.29 to 0.98)	0.56 (0.32 to 0.97)
	-2 to -1	0.83 (0.57 to 1.21)	0.72 (0.38 to 1.36)	0.50 (0.26 to 0.95)	0.52 (0.29 to 0.92)
	≥ -1	0.52 (0.35 to 0.80)	0.45 (0.24 to 0.87)	0.31 (0.16 to 0.60)	0.33 (0.18 to 0.59)
1 year	**< -3**	0.88 (0.47 to 1.65)	0.60 (0.35 to 1.02)	0.73 (0.43 to 1.22)	0.49 (0.30 to 0.80)
	-3 to -2	0.66 (0.34 to 1.31)	0.45 (0.26 to 0.81)	0.55 (0.31 to 0.98)	0.37 (0.22 to 0.63)
	-2 to -1	0.31 (0.15 to 0.67)	0.22 (0.11 to 0.43)	0.26 (0.12 to 0.51)	0.18 (0.09 to 0.33)
	≥ -1	0.26 (0.11 to 0.57)	0.17 (0.09 to 0.35)	0.21 (0.11 to 0.41)	0.14 (0.07 to 0.27)
2-4 years	**< -3**	0.50 (0.27 to 0.92)	0.43 (0.25 to 0.73)	0.26 (0.15 to 0.46)	0.32 (0.19 to 0.52)
	-3 to -2	0.21 (0.11 to 0.42)	0.18 (0.10 to 0.33)	0.11 (0.06 to 0.15)	0.13 (0.07 to 0.24)
	-2 to -1	0.09 (0.04 to 0.20)	0.08 (0.04 to 0.16)	0.05 (0.02 to 0.10)	0.06 (0.03 to 0.12)
	≥ -1	0.10 (0.05 to 0.22)	0.09 (0.04 to 0.17)	0.05 (0.03 to 0.11)	0.06 (0.03 to 0.12)
5-9 years	**< -3**	0.41 (0.25 to 0.68)	0.20 (0.11 to 0.35)	0.14 (0.08 to 0.27)	0.14 (0.08 to 0.26)
	-3 to -2	0.22 (0.12 to 0.40)	0.11 (0.06 to 0.20)	0.07 (0.04 to 0.15)	0.08 (0.04 to 0.15)
	-2 to -1	0.12 (0.06 to 0.23)	0.06 (0.03 to 0.11)	0.04 (0.02 to 0.08)	0.04 (0.02 to 0.08)
	≥ -1	0.08 (0.04 to 0.18)	0.04 (0.02 to 0.09)	0.03 (0.01 to 0.06)	0.03 (0.01 to 0.06)

Appendix Table S3 (a): Estimates of cumulative mortality at 3, 6 and 12 months after ART start from the model with CD4%

Age < 1 year

WHO Stage I or II

		CD4 percent <5%				CD4 percent 5-9.9%				CD4 percent ≥10%			
		Severe anaemia		Moderate/mild/no anaemia		Severe anaemia		Moderate/mild/no anaemia		Severe anaemia		Moderate/mild/no anaemia	
WAZ	**Months**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	23.1	17.5 to 30.1	17.4	13.6 to 22.0	17.4	13.2 to 22.7	12.9	10.2 to 16.3	14.0	10.8 to 18.0	10.4	8.4 to 12.8
<-3	6	31.3	24.1 to 40.0	23.8	18.9 to 29.9	23.9	18.4 to 30.7	18.0	14.3 to 22.4	19.4	15.1 to 24.7	14.5	11.8 to 17.7
<-3	12	38.5	30.1 to 48.4	29.7	23.8 to 36.8	29.8	23.1 to 37.8	22.6	18.2 to 28.0	24.4	19.2 to 30.7	18.4	15.0 to 22.3
-3 to -2	3	15.3	11.2 to 20.6	11.3	8.6 to 14.9	11.3	8.3 to 15.3	8.4	6.4 to 10.9	9.1	6.8 to 12.0	6.7	5.2 to 8.5
-3 to -2	6	21.1	15.6 to 28.1	15.8	12.0 to 20.5	15.8	11.7 to 21.1	11.7	9.0 to 15.1	12.7	9.6 to 16.6	9.4	7.4 to 11.8
-3 to -2	12	26.4	19.8 to 34.7	19.9	15.3 to 25.7	20.0	15.0 to 26.4	14.9	11.6 to 19.2	16.1	12.3 to 21.0	12.0	9.5 to 15.0
>=-2	3	9.4	6.9 to 12.9	7.0	5.3 to 9.1	7.0	5.1 to 9.4	5.1	4.0 to 6.5	5.5	4.2 to 7.3	4.1	3.3 to 5.0
>=-2	6	13.2	9.7 to 17.9	9.8	7.5 to 12.7	9.8	7.3 to 13.2	7.2	5.6 to 9.2	7.8	6.0 to 10.2	5.7	4.7 to 7.1
>=-2	12	16.8	12.4 to 22.6	12.5	9.6 to 16.1	12.5	9.3 to 16.7	9.2	7.3 to 11.7	10.0	7.7 to 13.1	7.4	6.0 to 9.0
WHO Stage III or IV													
WAZ		**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	28.5	22.8 to 35.3	21.6	17.9 to 25.9	21.6	17.2 to 27.0	16.2	13.5 to 19.4	17.5	14.4 to 21.3	13.0	11.3 to 15.0
<-3	6	38.1	31.0 to 46.2	29.4	24.7 to 34.7	29.4	23.7 to 36.1	22.3	18.8 to 26.4	24.1	19.9 to 28.9	18.1	15.9 to 20.6
<-3	12	46.3	38.2 to 55.2	36.3	30.8 to 42.5	36.3	29.6 to 44	27.9	23.7 to 32.7	30.0	25.1 to 35.7	22.8	20.1 to 25.8
-3 to -2	3	19.0	14.6 to 24.7	14.2	11.2 to 17.9	14.2	10.9 to 18.5	10.5	8.4 to 13.2	11.4	9.0 to 14.4	8.4	7.0 to 10.1
-3 to -2	6	26.1	20.2 to 33.3	19.7	15.7 to 24.5	19.7	15.2 to 25.3	14.7	11.8 to 18.3	15.9	12.7 to 19.9	11.8	9.9 to 14.1
-3 to -2	12	32.4	25.4 to 40.8	24.7	19.9 to 30.5	24.8	19.3 to 31.4	18.6	15.1 to 23	20.1	16.1 to 25.0	15.1	12.6 to 17.9
>=-2	3	11.9	8.9 to 15.9	8.8	6.9 to 11.2	8.8	6.6 to 11.7	6.5	5.1 to 8.1	7.0	5.5 to 9.0	5.1	4.3 to 6.2
>=-2	6	16.6	12.5 to 21.9	12.3	9.7 to 15.5	12.3	9.3 to 16.2	9.1	7.3 to 11.4	9.9	7.7 to 12.6	7.3	6.1 to 8.6
>=-2	12	20.9	15.8 to 27.3	15.7	12.4 to 19.6	15.7	11.9 to 20.5	11.6	9.4 to 14.4	12.6	9.9 to 16.0	9.3	7.9 to 11.0

Age 1 year

WHO Stage I or II

		CD4 percent <5%				CD4 percent 5-9.9%				CD4 percent ≥10%			
		Severe anaemia		derate/mild/no anaemia		Severe anaemia		derate/mild/no anaemia		Severe anaemia		derate/mild/no anaemia	
WAZ	**Months**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	18.5	13.9 to 24.3	13.8	10.7 to 17.6	13.8	10.4 to 18.1	10.2	8.0 to 12.9	11.1	8.5 to 14.3	8.2	6.5 to 10.1
<-3	6	25.3	19.3 to 32.8	19.1	14.9 to 24.2	19.1	14.6 to 24.7	14.3	11.3 to 17.9	15.4	12.0 to 19.7	11.4	9.2 to 14.1
<-3	12	31.5	24.3 to 40.2	24.0	18.9 to 30.1	24.0	18.5 to 30.8	18.1	14.4 to 22.5	19.5	15.3 to 24.8	14.6	11.8 to 17.9
-3 to -2	3	12.1	8.8 to 16.4	8.9	6.7 to 11.8	8.9	6.6 to 12.0	6.6	5.0 to 8.5	7.1	5.4 to 9.4	5.2	4.1 to 6.6
-3 to -2	6	16.8	12.4 to 22.5	12.5	9.5 to 16.4	12.5	9.3 to 16.7	9.2	7.1 to 11.9	10.0	7.6 to 13.1	7.4	5.8 to 9.3
-3 to -2	12	21.2	15.7 to 28.2	15.9	12.1 to 20.7	15.9	11.9 to 21.1	11.8	9.1 to 15.2	12.8	9.7 to 16.7	9.4	7.5 to 11.9
>=-2	3	7.4	5.4 to 10.2	5.4	4.1 to 7.1	5.4	4.0 to 7.4	4.0	3.1 to 5.1	4.3	3.3 to 5.7	3.2	2.5 to 3.9
>=-2	6	10.4	7.6 to 14.2	7.7	5.9 to 10.0	7.7	5.7 to 10.3	5.6	4.4 to 7.2	6.1	4.7 to 8.0	4.5	3.6 to 5.5
>=-2	12	13.3	9.8 to 18.0	9.8	7.6 to 12.8	9.9	7.3 to 13.2	7.3	5.7 to 9.2	7.9	6.0 to 10.3	5.8	4.7 to 7.1
WHO Stage III or IV													
WAZ		**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	22.9	18.2 to 28.7	17.2	14.2 to 20.8	17.2	13.7 to 21.5	12.8	10.7 to 15.4	13.9	11.4 to 16.9	10.3	8.9 to 11.9
<-3	6	31.1	25.0 to 38.2	23.7	19.7 to 28.3	23.7	19.1 to 29.2	17.8	15.0 to 21.1	19.2	15.9 to 23.2	14.4	12.5 to 16.5
<-3	12	38.3	31.2 to 46.4	29.5	24.8 to 35.0	29.6	24.0 to 36.1	22.5	19.0 to 26.4	24.2	20.1 to 29.0	18.2	16.0 to 20.7
-3 to -2	3	15.1	11.5 to 19.7	11.2	8.8 to 14.2	11.2	8.6 to 14.6	8.3	6.6 to 10.4	9.0	7.1 to 11.3	6.6	5.5 to 8.0
-3 to -2	6	20.9	16.1 to 26.9	15.6	12.4 to 19.6	15.7	12.1 to 20.1	11.6	9.4 to 14.4	12.6	10.0 to 15.8	9.3	7.8 to 11.1
-3 to -2	12	26.2	20.4 to 33.3	19.8	15.8 to 24.6	19.8	15.4 to 25.2	14.8	12.0 to 18.2	16.0	12.8 to 19.9	11.9	10.0 to 14.1
>=-2	3	9.4	7.0 to 12.6	6.9	5.4 to 8.8	6.9	5.2 to 9.2	5.1	4.0 to 6.3	5.5	4.3 to 7.0	4.0	3.3 to 4.8
>=-2	6	13.1	9.8 to 17.4	9.7	7.6 to 12.3	9.7	7.4 to 12.8	7.1	5.7 to 8.9	7.8	6.1 to 9.9	5.7	4.8 to 6.8
>=-2	12	16.7	12.6 to 21.9	12.4	9.8 to 15.6	12.4	9.4 to 16.2	9.2	7.4 to 11.4	9.9	7.8 to 12.6	7.3	6.2 to 8.7

Age 2-4 years

WHO Stage I or II

		CD4 percent <5%				CD4 percent 5-9.9%				CD4 percent ≥10%			
		Severe anaemia		derate/mild/no anaemia		Severe anaemia		derate/mild/no anaemia		Severe anaemia		derate/mild/no anaemia	
WAZ	**Months**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	8.8	6.5 to 11.8	6.5	5.0 to 8.4	6.5	4.8 to 8.6	4.7	3.7 to 6.1	5.2	3.9 to 6.8	3.8	3.0 to 4.8
<-3	6	12.3	9.2 to 16.4	9.1	7.1 to 11.7	9.1	6.9 to 12.1	6.7	5.3 to 8.5	7.3	5.5 to 9.6	5.3	4.2 to 6.7
<-3	12	15.7	11.8 to 20.7	11.7	9.1 to 14.9	11.7	8.8 to 15.3	8.6	6.8 to 10.9	9.3	7.1 to 12.2	6.9	5.5 to 8.6
-3 to -2	3	5.6	4.1 to 7.7	4.1	3.1 to 5.5	4.1	3.0 to 5.6	3.0	2.3 to 3.9	3.3	2.4 to 4.4	2.4	1.9 to 3.1
-3 to -2	6	8.0	5.8 to 10.8	5.8	4.4 to 7.7	5.9	4.3 to 7.9	4.3	3.3 to 5.5	4.7	3.5 to 6.2	3.4	2.7 to 4.3
-3 to -2	12	10.2	7.5 to 13.8	7.5	5.7 to 9.8	7.5	5.6 to 10.1	5.5	4.3 to 7.1	6.0	4.5 to 7.9	4.4	3.4 to 5.6
>=-2	3	3.4	2.5 to 4.7	2.5	1.9 to 3.2	2.5	1.8 to 3.4	1.8	1.4 to 2.3	2.0	1.5 to 2.6	1.4	1.2 to 1.8
>=-2	6	4.9	3.5 to 6.6	3.5	2.7 to 4.6	3.6	2.6 to 4.8	2.6	2.0 to 3.3	2.8	2.1 to 3.7	2.1	1.7 to 2.5
>=-2	12	6.2	4.6 to 8.5	4.6	3.5 to 5.9	4.6	3.4 to 6.1	3.3	2.7 to 4.2	3.6	2.8 to 4.8	2.7	2.2 to 3.3
WHO Stage III or IV													
WAZ		**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	11.1	8.6 to 14.2	8.2	6.6 to 10.1	8.2	6.4 to 10.5	6.0	4.9 to 7.3	6.5	5.2 to 8.2	4.8	4.0 to 5.7
<-3	6	15.5	12.1 to 19.7	11.5	9.4 to 14.0	11.5	9.0 to 14.6	8.5	7.0 to 10.3	9.2	7.4 to 11.5	6.8	5.7 to 8.0
<-3	12	19.6	15.4 to 24.7	14.6	12.0 to 17.8	14.6	11.6 to 18.5	10.9	9.0 to 13.1	11.8	9.4 to 14.6	8.7	7.4 to 10.2
-3 to -2	3	7.1	5.4 to 9.5	5.2	4.1 to 6.7	5.2	4.0 to 6.9	3.8	3.0 to 4.8	4.2	3.2 to 5.4	3.0	2.5 to 3.7
-3 to -2	6	10.1	7.6 to 13.2	7.4	5.8 to 9.4	7.4	5.7 to 9.7	5.4	4.3 to 6.8	5.9	4.6 to 7.5	4.3	3.6 to 5.3
-3 to -2	12	12.8	9.8 to 16.7	9.5	7.5 to 11.9	9.5	7.3 to 12.4	7.0	5.6 to 8.7	7.6	5.9 to 9.6	5.6	4.6 to 6.7
>=-2	3	4.3	3.2 to 5.9	3.2	2.5 to 4.1	3.2	2.4 to 4.2	2.3	1.8 to 2.9	2.5	1.9 to 3.3	1.8	1.5 to 2.2
>=-2	6	6.2	4.6 to 8.2	4.5	3.5 to 5.7	4.5	3.4 to 6.0	3.3	2.6 to 4.1	3.6	2.8 to 4.6	2.6	2.2 to 3.1
>=-2	12	7.9	5.9 to 10.5	5.8	4.6 to 7.3	5.8	4.4 to 7.7	4.3	3.4 to 5.3	4.6	3.6 to 5.9	3.4	2.8 to 4.0

Age 5-10 years

WHO Stage I or II

		CD4 percent <5%				CD4 percent 5-9.9%				CD4 percent ≥10%			
		Severe anaemia		derate/mild/no anaemia		Severe anaemia		derate/mild/no anaemia		Severe anaemia		derate/mild/no anaemia	
WAZ	**Months**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	6.2	4.6 to 8.3	4.5	3.5 to 5.8	4.5	3.3 to 6.1	3.3	2.6 to 4.2	3.6	2.7 to 4.8	2.6	2.1 to 3.3
<-3	6	8.7	6.5 to 11.6	6.4	5.0 to 8.2	6.4	4.8 to 8.6	4.7	3.7 to 6.0	5.1	3.8 to 6.8	3.7	2.9 to 4.7
<-3	12	11.1	8.3 to 14.8	8.2	6.5 to 10.4	8.2	6.1 to 11.0	6.0	4.7 to 7.7	6.6	4.9 to 8.7	4.8	3.8 to 6.1
-3 to -2	3	3.9	2.9 to 5.4	2.9	2.2 to 3.8	2.9	2.1 to 3.9	2.1	1.6 to 2.7	2.3	1.7 to 3.1	1.7	1.3 to 2.1
-3 to -2	6	5.6	4.1 to 7.6	4.1	3.1 to 5.3	4.1	3.0 to 5.6	3.0	2.3 to 3.9	3.2	2.4 to 4.4	2.4	1.8 to 3.0
-3 to -2	12	7.2	5.3 to 9.7	5.3	4.0 to 6.8	5.3	3.9 to 7.2	3.8	3.0 to 5.0	4.2	3.1 to 5.6	3.1	2.4 to 3.9
>=-2	3	2.4	1.7 to 3.3	1.7	1.3 to 2.2	1.7	1.3 to 2.4	1.3	1 .0 to 1.6	1.4	1.0 to 1.8	1.0	0.8 to 1.2
>=-2	6	3.4	2.5 to 4.6	2.5	1.9 to 3.2	2.5	1.8 to 3.4	1.8	1.4 to 2.3	2.0	1.5 to 2.6	1.4	1.1 to 1.8
>=-2	12	4.4	3.2 to 5.9	3.2	2.5 to 4.1	3.2	2.4 to 4.3	2.3	1.8 to 2.9	2.5	1.9 to 3.4	1.8	1.5 to 2.3
WHO Stage III or IV													
WAZ		**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	7.8	6.1 to 10.0	5.7	4.7 to 7.0	5.7	4.4 to 7.5	4.2	3.4 to 5.1	4.6	3.6 to 5.9	3.3	2.8 to 4.0
<-3	6	11.0	8.6 to 14.0	8.1	6.7 to 9.8	8.1	6.3 to 10.5	5.9	4.9 to 7.2	6.5	5.1 to 8.2	4.7	4.0 to 5.7
<-3	12	14.0	11.0 to 17.7	10.4	8.6 to 12.5	10.4	8.1 to 13.3	7.6	6.3 to 9.3	8.3	6.5 to 10.5	6.1	5.1 to 7.3
-3 to -2	3	5.0	3.8 to 6.6	3.7	2.9 to 4.6	3.7	2.7 to 4.9	2.7	2.1 to 3.4	2.9	2.2 to 3.8	2.1	1.7 to 2.6
-3 to -2	6	7.1	5.4 to 9.3	5.2	4.1 to 6.5	5.2	3.9 to 6.9	3.8	3.0 to 4.7	4.1	3.2 to 5.4	3.0	2.5 to 3.7
-3 to -2	12	9.1	6.9 to 11.8	6.7	5.4 to 8.3	6.7	5.0 to 8.8	4.9	3.9 to 6.1	5.3	4.1 to 6.9	3.9	3.2 to 4.7
>=-2	3	3.0	2.2 to 4.1	2.2	1.8 to 2.8	2.2	1.6 to 3.0	1.6	1.3 to 2.0	1.8	1.3 to 2.3	1.3	1.0 to 1.6
>=-2	6	4.3	3.2 to 5.8	3.1	2.5 to 3.9	3.1	2.3 to 4.2	2.3	1.8 to 2.9	2.5	1.9 to 3.3	1.8	1.5 to 2.2
>=-2	12	5.5	4.1 to 7.4	4.1	3.2 to 5.0	4.1	3.0 to 5.4	3.0	2.4 to 3.7	3.2	2.5 to 4.2	2.3	1.9 to 2.8

Appendix Table S3 (b): Estimates of cumulative mortality at 3, 6 and 12 months after ART start from the model without CD4%

Age < 1 year

WHO Stage I or II

		Severe anaemia		Moderate/mild/no anaemia	
WAZ	**Months**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	15.8	12.3 to 20.2	11.6	9.4 to 14.2
<-3	6	21.8	17.2 to 27.5	16.1	13.2 to 19.5
<-3	12	27.3	21.7 to 34.0	20.3	16.8 to 24.5
-3 to -2	3	10.0	7.5 to 13.1	7.2	5.7 to 9.1
-3 to -2	6	13.9	10.6 to 18.1	10.1	8.1 to 12.7
-3 to -2	12	17.6	13.5 to 22.8	12.9	10.3 to 16.1
>=-2	3	6.0	4.5 to 7.9	4.3	3.5 to 5.3
>=-2	6	8.4	6.4 to 11.0	6.1	5.0 to 7.5
>=-2	12	10.8	8.3 to 14.0	7.8	6.4 to 9.5
WHO Stage III or IV					
WAZ		**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	19.7	16.3 to 23.8	14.5	12.7 to 16.5
<-3	6	26.9	22.5 to 32.0	20.1	17.8 to 22.6
<-3	12	33.4	28.2 to 39.3	25.2	22.4 to 28.2
-3 to -2	3	12.5	9.9 to 15.7	9.1	7.6 to 10.9
-3 to -2	6	17.4	13.9 to 21.6	12.8	10.7 to 15.1
-3 to -2	12	21.9	17.7 to 27.1	16.2	13.7 to 19.1
>=-2	3	7.6	5.9 to 9.7	5.5	4.6 to 6.5
>=-2	6	10.6	8.3 to 13.5	7.7	6.5 to 9.1
>=-2	12	13.5	10.7 to 17.1	9.9	8.3 to 11.7

Age 1 year

WHO Stage I or II

		Severe anaemia		Moderate/mild/no anaemia	
WAZ	**Months**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	12.5	9.7 to 16.0	9.1	7.4 to 11.2
<-3	6	17.4	13.6 to 22.0	12.7	10.4 to 15.5
<-3	12	21.9	17.3 to 27.5	16.2	13.3 to 19.6
-3 to -2	3	7.8	5.9 to 10.3	5.6	4.4 to 7.1
-3 to -2	6	11.0	8.4 to 14.3	8.0	6.3 to 10.0
-3 to -2	12	14.0	10.7 to 18.1	10.2	8.1 to 12.8
>=-2	3	4.7	3.5 to 6.1	3.4	2.7 to 4.1
>=-2	6	6.6	5.0 to 8.6	4.8	3.9 to 5.8
>=-2	12	8.5	6.5 to 11.0	6.1	5.0 to 7.5
WHO Stage III or IV					
WAZ		**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	15.7	12.9 to 19.0	11.5	10.0 to 13.1
<-3	6	21.6	18.0 to 25.8	16.0	14.1 to 18.1
<-3	12	27.1	22.7 to 32.1	20.2	17.9 to 22.7
-3 to -2	3	9.9	7.8 to 12.4	7.1	6.0 to 8.6
-3 to -2	6	13.8	11.0 to 17.2	10.0	8.4 to 11.9
-3 to -2	12	17.5	14.1 to 21.6	12.8	10.8 to 15.2
>=-2	3	5.9	4.6 to 7.6	4.3	3.6 to 5.1
>=-2	6	8.3	6.5 to 10.6	6.0	5.1 to 7.2
>=-2	12	10.7	8.4 to 13.5	7.7	6.5 to 9.1

Age 2-4 years

WHO Stage I or II

		Severe anaemia		Moderate/mild/no anaemia	
WAZ	**Months**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	6.1	4.6 to 7.9	4.4	3.5 to 5.5
<-3	6	8.6	6.6 to 11.1	6.2	5.0 to 7.7
<-3	12	11.0	8.5 to 14.1	8.0	6.4 to 9.8
-3 to -2	3	3.7	2.8 to 5.0	2.7	2.1 to 3.4
-3 to -2	6	5.3	4.0 to 7.0	3.8	3.0 to 4.8
-3 to -2	12	6.8	5.2 to 9.0	4.9	3.9 to 6.2
>=-2	3	2.2	1.7 to 2.9	1.6	1.3 to 2.0
>=-2	6	3.2	2.4 to 4.1	2.3	1.8 to 2.8
>=-2	12	4.1	3.1 to 5.3	2.9	2.4 to 3.6

WHO Stage III or IV

WAZ		**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	7.7	6.2 to 9.6	5.6	4.7 to 6.5
<-3	6	10.8	8.7 to 13.3	7.8	6.7 to 9.1
<-3	12	13.8	11.2 to 16.9	10.0	8.7 to 11.6
-3 to -2	3	4.8	3.7 to 6.1	3.4	2.8 to 4.1
-3 to -2	6	6.7	5.3 to 8.5	4.8	4.0 to 5.8
-3 to -2	12	8.6	6.8 to 10.9	6.2	5.2 to 7.5
>=-2	3	2.8	2.2 to 3.6	2.0	1.7 to 2.4
>=-2	6	4.0	3.1 to 5.2	2.9	2.4 to 3.4
>=-2	12	5.2	4.0 to 6.6	3.7	3.1 to 4.4

Age < 5-10 years

WHO Stage I or II

		Severe anaemia		Moderate/mild/no anaemia	
WAZ	**Months**	**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	4.6	3.5 to 6.0	3.3	2.6 to 4.1
<-3	6	6.5	4.9 to 8.5	4.7	3.8 to 5.8
<-3	12	8.3	6.3 to 10.8	6.0	4.8 to 7.4
-3 to -2	3	2.8	2.1 to 3.8	2.0	1.6 to 2.6
-3 to -2	6	4.0	3.0 to 5.3	2.9	2.3 to 3.6
-3 to -2	12	5.1	3.9 to 6.8	3.7	2.9 to 4.6
>=-2	3	1.7	1.2 to 2.2	1.2	1.0 to 1.5
>=-2	6	2.4	1.8 to 3.1	1.7	1.4 to 2.1
>=-2	12	3.1	2.3 to 4.0	2.2	1.8 to 2.7

WHO Stage III or IV

WAZ		**Probability (%)**	**95% CI**	**Probability (%)**	**95% CI**
<-3	3	5.8	4.6 to 7.3	4.2	3.6 to 4.9
<-3	6	8.2	6.5 to 10.2	5.9	5.1 to 6.9
<-3	12	10.5	8.4 to 13.0	7.6	6.5 to 8.8
-3 to -2	3	3.6	2.8 to 4.6	2.6	2.1 to 3.1
-3 to -2	6	5.1	3.9 to 6.5	3.6	3.0 to 4.4
-3 to -2	12	6.5	5.1 to 8.3	4.7	3.9 to 5.6
>=-2	3	2.1	1.6 to 2.8	1.5	1.3 to 1.8
>=-2	6	3.0	2.3 to 3.9	2.2	1.8 to 2.6
>=-2	12	3.9	3.0 to 5.0	2.8	2.3 to 3.3

Table S4: Characteristics of children included in the main analysis compared to those excluded due to being LTFU or TFO within the first 6 months of treatment. P-values derived from Wilcoxon rank sum tests and chi^2 tests for differences in medians and proportions between the 2 groups for continuous variables and categorical variables respectively.

	Patients LTFU or TFO in the first 6 months of treatment		
	No (N=10875)	Yes (N=1780)	p-value
AGE			
Median age in months (IQR)	47 (21 to 80)	27 (14 to 64)	<0.001
<24 months of age (%)	29%	46%	<0.001
STAGE			
WHO Stage III/IV disease (%)	72%	78%	<0.001
CD4 PERCENT			
Median CD4% (IQR)	13.0 (8.3 to 18.5)	14.3 (9.4 to 21.2)	<0.001
ANAEMIA			
Severe anaemia (%)	9%	13%	<0.001
WAZ			
Median WAZ (IQR)	-2.03 (-3.23 to -1.01)	-2.64 (-3.99 to -1.40)	<0.001
WAZ <-3 (%)	29%	43%	<0.001

2.4 Virologic Failure and Second-Line Antiretroviral Therapy in Children in South Africa—The IeDEA Southern Africa Collaboration

Paper overview

This paper reports on the probability and predictors of confirmed virological failure (VF) (>1000 copies/ml) for up to three years on ART among children treated at South African IeDEA SA sites. It also describes the proportion of children with VF switched to second-line therapy and predictors of switch.

Contribution to the thesis and novelty

This paper examines the measurement of treatment success in South Africa and thus addresses the third objective of the thesis. It remains the largest published study of VF in children and one of two studies152 to provide estimates of confirmed VF over an extended period of time in the context of a programme with routine HIV-RNA monitoring. The finding that 20% of children will meet the definition of VF by three years after ART initiation is useful for programme planning. The paper also identified that VF was more likely in children treated with NVP- based compared to LPV/r-based regimens irrespective of PMTCT exposure, a finding that has now been confirmed by the P1060 trial.130 Triple ART including unboosted RTV was also associated with a higher risk of VF compared to EFV-based or LPV/r-based regimens. Delayed switching and between-site heterogeneity in switching practice highlighted the need for clearer guidelines for management of patients with unsuppressed viral load.

Role of the candidate

The candidate was responsible for all data management to generate the IeDEA paediatric data set for analysis. She was solely responsible for the analysis. She presented the data at the 1st International Workshop on HIV Pediatrics and the International AIDS Society Conference in 2009. She drafted the manuscript, incorporated input from co-authors and was responsible for finalising and submitting the final version of the manuscript for publication.

Publication status

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Virologic Failure and Second-Line Antiretroviral Therapy in Children in South Africa—The IeDEA Southern Africa Collaboration

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Background: With expanding pediatric antiretroviral therapy (ART) access, children will begin to experience treatment failure and require second-line therapy. We evaluated the probability and determinants of virologic failure and switching in children in South Africa.

Methods: Pooled analysis of routine individual data from children who initiated ART in 7 South African treatment programs with 6-monthly viral load and CD4 monitoring produced Kaplan-Meier estimates of probability of virologic failure (2 consecutive unsuppressed viral loads with the second being >1000 copies/mL, after ≥24 weeks of therapy) and switch to second-line. Cox-proportional hazards models stratified by program were used to determine predictors of these outcomes.

Results: The 3-year probability of virologic failure among 5485 children was 19.3% (95% confidence interval: 17.6 to 21.1). Use of nevirapine or ritonavir alone in the initial regimen (compared with efavirenz) and exposure to prevention of mother to child transmission regimens were independently associated with failure [adjusted hazard ratios (95% confidence interval): 1.77 (1.11 to 2.83), 2.39 (1.57 to 3.64) and 1.40 (1.02 to 1.92), respectively]. Among 252 children with ≥1 year follow-up after failure, 38% were switched to second-line. Median (interquartile range) months between failure and switch was 5.7 (2.9–11.0).

Conclusions: Triple ART based on nevirapine or ritonavir as a single protease inhibitor seems to be associated with a higher risk of virologic failure. A low proportion of virologically failing children were switched.

Key Words: antiretroviral therapy, children, resource-limited setting, second-line therapy, virologic failure

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INTRODUCTION

With expanding access to antiretroviral therapy (ART) for HIV-infected children, increasing numbers are likely to experience treatment failure and require second-line regimens. Before 2010, WHO pediatric guidelines did not define virologic failure (VF) and viral load monitoring remains unavailable in most resource-limited settings.[1,2] In contrast, industrialized country guidelines stipulate strict viral load criteria for switching at thresholds as low as 2 consecutive measurements >400 copies per milliliter.[3,4]

Due to poor access to viral load monitoring in resource-limited settings, there is limited published data on VF in children.[1] Existing studies are limited by cohort size, exclusive

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The members of the IeDEA Southern Africa Steering Group are listed in the Appendix.

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use of non-nucleoside reverse transcriptase inhibitor (NNRTI)–based regimens and/or failure definitions based on a single elevated viral load measurement.[5–9] Poor access to and lack of experience with second-line therapy, and national policies that may restrict second-line use, have resulted in low numbers and proportions of children being switched even in larger cohorts.[5,6,10–14] Predictors of which children are switched in resource-limited settings have therefore not been examined.

The International epidemiologic Databases to Evaluate AIDS (IeDEA) Southern Africa collaboration includes 7 South African pediatric ART programs with data on more than 6000 children who had initiated treatment before 2008.[15,16] Regular viral load monitoring (at least 6-monthly) is part of routine ART care in South Africa.[17] However, until 2010, national pediatric treatment guidelines did not provide clear direction on management of VF.[17] We aimed to examine the probability of VF and its associations, and, in children with VF, to determine the probability of switching to second-line and identify factors that predicted which children were switched.

METHODS

Study Design, Setting and Population

Data for this multicenter analysis were collected prospectively at sites. Each site has institutional ethical approval for contribution of data to IeDEA analyses and transferred data anonymously to the IeDEA data center between May 2007 and February 2008. The analysis included treatment-naive children (<16 years) initiating ART with ≥3 antiretroviral drugs between June 1999 and February 2008.

Treatment Regimens

All treatment sites are part of the South African national treatment program that commenced in April 2004 with the following first-line regimen guidelines: stavudine (d4T), lamivudine (3TC), and either efavirenz (EFV) or if <3 years/<10kg, a protease inhibitor (PI).[17] For most children, this was lopinavir/ritonavir (LPV/r), however, ritonavir alone (RTV) was recommended for children with tuberculosis or <6 months old.[17] The latter 2 recommendations changed during 2007; LPV/r with additional RTV boosting was introduced for children with tuberculosis, and LPV/r dosing recommendations became available for children <6 months old.[18,19] Some cohorts introduced these practices before 2007, and also used more varied regimens before commencement of the national program, including NNRTI-based regimens in children <3 years old, RTV alone as the "third drug" in children of all ages, and zidovudine (ZDV) instead of d4T. National guidelines were otherwise adhered to in all provinces and permitted restricted individual drug substitution for intolerance or nonavailability of the recommended drug in suitable formulation.[17]

National guidelines second-line regimens were ZDV + didanosine with either LPV/r (EFV-based first line), or an NNRTI (PI-based first line).[17] The NNRTI was nevirapine (NVP) for children <3 years old at switch, and EFV for older children.[17]

Decisions to switch could be made by the program clinician without formal Department of Health approval. Second-line regimens were accessible at all sites.

National guidelines advised single dose NVP (sdNVP) for mother and infant for prevention of mother to child transmission (PMTCT), with triple ART for pregnant women with WHO stage 4 disease or CD4 ≤200 cells per microliter.[20,21] However, in the Western Cape province, PMTCT programs began before national roll-out, with a variety of regimens being used including sdNVP or ZDV from 34 weeks ± sdNVP. Similarly, after national implementation of the sdNVP regimen, the Western Cape province and McCord Hospital used more effective PMTCT regimens (Table 1).[22]

Key Variables

Sociodemographic and clinical data at ART start included age, gender, clinical stage [stage 3 (2002 3-stage WHO classification) and stages 3/4 (2005 4-stage WHO classification) were combined],[23,24] exposure to PMTCT regimens and starting regimen. Weight, viral load, CD4 absolute count and percent were available at ART start and 6-monthly thereafter. Access to viral load and CD4 measurement was similar across sites. Viral load measurements were performed using Amplicor 1.5 (Roche Diagnostics, Basel, Switzerland) or NucliSens EasyQ assays (bioMerieux, Durham, NC), which have good comparability.[25] Severe immune suppression was defined according to WHO guidelines.[2] "Baseline" measurements were those taken closest to ART initiation and within 6 months (CD4 and viral load) or 2 weeks (weight) prior, to 1 week after commencing ART. Sex-adjusted weight-for-age *z* scores (WAZ) were calculated using WHO 2007 reference values for children ≤10 years of age.[26]

Outcomes

VF was defined as 2 consecutive (≤12 months apart) viral load measurements ≥400 copies per milliliter with the second being >1000 copies per milliliter, and both taken after 24 weeks on ART, and not during a treatment interruption. Sensitivity analyses used different thresholds (400, 5000 and 10,000 copies/mL) to define VF. Children were considered to have switched to second-line if any of the following occurred <1 year after a viral load measurement >400 copies per milliliter: (1) commencement of ≥2 new drugs including a class switch from PI to NNRTI or vice versa; (2) class switch from NNRTI to PI or vice versa only, with reason documented as treatment failure; or (3) change of both NRTIs and change from RTV to LPV/r with reason documented as treatment failure. Immunologic failure was defined according to South African guidelines criteria for switching as either CD4% below baseline value after 24 weeks of therapy or CD4% <50% of peak value during preceding treatment.

Analysis

Continuous and categorical variables were summarized using medians and interquartile ranges (IQR) and proportions, respectively. Kaplan-Meier probabilities of virologic and immunologic failure and switch were estimated. Predictors of failure and switch were determined using Cox-proportional

TABLE 1. Characteristics of Sites Providing ART for Children

Cohort Name and Location	Main Level of Care Provided	Type of Clinic and Payment	Target Population	Most Likely PMTCT Intervention*	First Year of Pediatric ART Provision	Number of Children on ART
Harriet Shezi, Chris Hani Baragwanath Hospital, Soweto	All levels	Public and research, free ART	Children only	sdNVP to mother and infant	2001	1,865
Rahima Moosa Mother and Child Hospital, Johannesburg	All levels	Public, free ART	Children and pregnant women	sdNVP to mother and infant	1999	938
Red Cross Children's Hospital, Cape Town	Tertiary	Public and research, free ART	Children only	ZDV from 34 weeks gestation + sdNVP to mother and infant	2001	828
Tygerberg Hospital, Cape Town	Tertiary	Public, free ART	Adults and children, separate clinics	ZDV from 34 weeks gestation + sdNVP to mother and infant	2000	591
Khayelitsha Community Health Centre, Cape Town	Primary	Public, free ART	Adults and children, separate clinics	ZDV from 34 weeks gestation + sdNVP to mother and infant	2001	650
Gugulethu Community Health Centre, Cape Town	Primary	Public and research, free ART	Adults and children, separate clinics	ZDV from 34 weeks gestation + sdNVP to mother and infant	2001	209
McCord Hospital, Durban	Secondary	Government subsidized not for profit hospital, small copayment	Adults and children, combined clinics	sdNVP to mother and infant	2003	404
Total	—	—	—	—	—	5485

*This is the PMTCT intervention available through the public health system within the province in which each site is located. It is not necessarily the intervention that each individual child attending that facility received, as individual program PMTCT regimens varied and mothers may have accessed antenatal care in other provinces/programs.

hazards models stratified by site to account for between-site heterogeneity. Only children with ≥6 months of follow-up after failure were included in the switch model. The following variables were included *a priori* in multivariable models: age, gender, and immune suppression at ART initiation (failure model); age, gender and treatment duration at time of failure (switch model). Thereafter, multivariable models retained variables with adjusted P values <0.1. In comparison to known lack of PMTCT exposure, missing PMTCT exposure information had no effect on failure, so these categories were combined. Separate failure models were generated including and excluding WAZ and stage, as missing data for these variables and exclusion of children >10 years old due to lack of WHO WAZ reference values substantially reduced the number of children that could be included in the model. The proportional hazards assumption was met for all models. Statistical analyses were performed using Stata version 10 (STATA Corporation, College Station, TX).

RESULTS

Data from all South African IeDEA sites providing pediatric ART were included (Table 1). This comprised 6266 children of whom 781 (12%) were excluded for the following reasons: missing or inconsistent baseline data (n = 85), non-naïve (n = 39), mono/dual therapy (n = 64) and starting regimen not recorded (n = 593). The final dataset comprised 5485 children (49% female) with median (IQR) follow-up of 16 (6–29) months. During follow-up, 344 (6%) children died, 411 (7%) were lost to follow-up and 885 (16%) were transferred out after median durations of 1.5, 5.8, and 12.9 months, respectively. There were 13,877 viral load and 12,749 CD4 percent measurements during follow-up with median (IQR) intervals between measurements of 168 (104–190) and 168 (126–197) days, respectively.

Most children were severely ill at ART start (Table 2). The median (IQR) age of children commencing ART was 42 (15–82) months. The NRTI backbone was d4T/3TC for 89% of children. The most common "third" drugs were EFV (55%), LPV/r (33%), RTV alone (7%), and NVP (5%).

Virologic Failure

The estimated probability of failure (second elevated value ≥ 1,000 copies/mL) by 36 months was 19.3% [95% confidence interval (CI): 17.6 to 21.1, Fig. 1]. Of the 523 children with VF, 311 (59%) had never been virologically suppressed. Among these children whose viral load was never <400 copies per milliliter, 217 had both baseline and ≥1 subsequent viral load measurement performed between 6 and 15 months on ART, and 121 (55%) showed a virologic response to therapy (≥1 $\log_{10}$ reduction from baseline viral load during the first year on ART). Using different thresholds for the second unsuppressed viral load, the 36-month estimated probability of failure ranged from 14.6% (95% CI: 13.1 to 16.3) (cut-off = 10,000 copies/mL) to 21.1% (95% CI: 19.3 to 23.0) (cut-off = 400 copies/mL) (Fig. 1). By 1 year and 3 years on ART, the estimated probabilities of a single viral load measurement >1,000 copies

TABLE 2. Characteristics of Children at ART Initiation, Failure (Second Consecutive Unsuppressed Viral Load > 1,000 Copies/mL), and Switch

Characteristic	All Children, n = 5485	Children With VF, n = 523	Children With VF Switched to Second-Line, n = 145*
Female	2674 (49%)	235 (45%)	51 (35%)
Median (IQR) age (mo)			
At ART start	42 (15–82)	37 (13–86)	60 (16–94)
At failure	NA	51 (26–103)	74 (29–108)
<12 months of age at ART start	1158 (21%)	123 (23%)	26 (18%)
Severe immune suppression			
At ART start	3690/4577 (81%)	384/447 (86%)	119/128 (93%)
At failure	NA	184/493 (37%)	57/138 (41%)
Median (IQR) CD4 percent			
At ART start, n	12 (7–17)	10 (5–15), 408	7 (3–12), 118
At failure, n	NA	20 (14–26), 464	18 (12–25), 127
WHO stage 3 or 4 at ART start	2887/3832 (75%)	275/374 (74%)	88/116 (76%)
Viral load > 1 million copies/mL			
At ART start	777/3745 (21%)	110/388 (28%)	29/111 (26%)
At failure	NA	13/524 (2%)	4/145 (3%)
Median (IQR) log viral load			
At ART start, n	5.3 (4.7–5.9)	5.6 (5.0–6.1), 388	5.6 (5.0–6.1), 111
At failure; n	NA	4.2 (3.7–4.9), 524	4.4 (3.9–5.1), 145
Weight-for-age *z* score < −2			
At ART start	1759/3646 (48%)	170/329 (52%)	46/89 (52%)
At failure	NA	73/385 (19%)	22/103 (21%)
Median (IQR) weight-for-age *z* score			
At ART start, n	−1.93 (−3.36 to −0.96), 3646	−2.08 (−3.43 to −1.07), 329	−2.14 (−3.31 to −0.96), 89
At failure, n	NA	−0.87 (−1.74 to −0.12), 385	−0.79 (−1.74 to −0.13), 103
PMTCT exposure			
Exposed	556 (10%)	67 (13%)	14 (10%)
Known unexposed	1644 (30%)	176 (34%)	61 (42%)
Exposure status unknown	3285 (60%)	280 (53%)	70 (48%)
First-line regimen			
d4T and 3TC based	4857 (89%)	420 (80%)	103 (71%)
Nevirapine as third drug	254 (5%)	45 (9%)	20 (14%)
Efavirenz as third drug	3030 (55%)	251 (48%)	88 (61%)
LPV/r as third drug	1819 (33%)	140 (27%)	10 (7%)
Ritonavir alone as third drug	382 (7%)	88 (17%)	27 (19%)

*Eight children were switched to second-line who did not meet criteria for VF but had viral load >400 copies per milliliter preceding switch. These children are excluded from this column.

per milliliter were 16.9% (95% CI: 15.8 to 18.1) and 32.1% (95% CI: 30.2 to 34.1), respectively. By 3 years, 384 children had immunologic failure with an estimated cumulative probability of 12.6% (95% CI: 11.3 to 13.0). The probability of immunologic failure was lower than that for all definitions of VF, except in the early months as the immunologic failure definition did not require confirmation.

In the multivariable model of associations with VF, viral load >1 million copies per milliliter at ART initiation was the only disease characteristic that predicted failure (Table 3). After adjustment for gender, age, baseline viral load, and immune suppression, failure risk was increased with use of either NVP [adjusted hazard ratio (aHR): 1.77; 95%CI: 1.11 to 2.83] or RTV alone (aHR: 2.39; 95% CI: 1.57 to 3.64) compared with EFV in the initial regimen. Known PMTCT exposure was also associated with failure (aHR: 1.40; 95% CI: 1.02 to 1.92). Results were very similar using different thresholds to define VF. Results were also similar if additionally adjusted for WHO stage and WAZ, neither of which remained independently associated with failure. A further model was developed excluding children with virologic nonresponse, and results were similar except for an attenuated effect of PMTCT. Results of all additional analyses are shown in (see **Table, Supplemental Digital Content 1**, http://links.lww.com/QAI/A146).

Switching to Second-Line

The estimated probability of switching to second-line by 3 years after ART initiation for all children was 6.2% (95% CI: 5.2 to 7.5, Fig. 1). Of the 153 children switched,

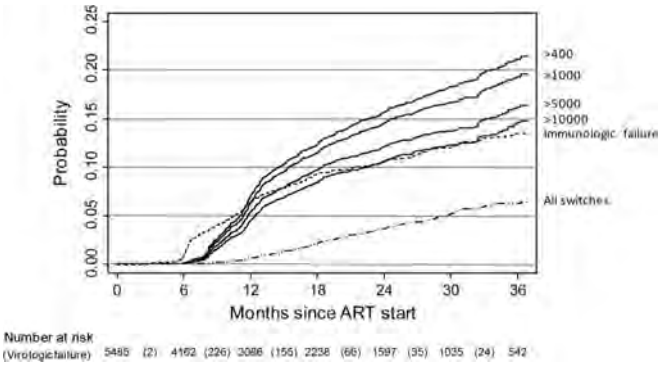

FIGURE 1. Kaplan-Meier probability of virologic failure using different viral load values (measured in copies/mL) to define failure, and immunologic failure and switch. Solid lines indicate VF defined as 2 consecutive unsuppressed viral loads with the second viral load being above the threshold value indicated; dashed line indicates immunologic failure; dash-dot line indicates switch to second-line. Note: The numbers in parentheses in the risk table refer to VF events defined as 2 consecutive viral load measurements >400 copies per milliliter with second viral load >1,000 copies per milliliter, and this is used as the definition of failure in analyses.

8 did not meet the VF criteria because there was only 1 unsuppressed viral load measurement (n = 7), or consecutive measurements were both before 24 weeks on ART (n = 1). Of 252 children with ≥1 year of follow-up after failure, 38% (95% CI: 32% to 45%) were switched. The median (IQR) time to switch from failure was 5.7 (2.9–11.0) months and from first unsuppressed viral load was 9.5 (5.5–14.6) months. The median (IQR) interval between consecutive unsuppressed viral load measurements was 3.2 (2.5–5.4) months.

Most second-line regimens included didanosine as one of the NRTIs (108 of 153; 71%). Other NRTIs included ZDV (66%), 3TC (25%); d4T (21%); abacavir (13%), and tenofovir (1%). The "third drug" in the regimen was LPV/r for 74% of children.

After adjustment for age at ART initiation, gender and treatment duration, children with more severe or progressive disease from the time of failure (higher viral load, CD4% <25 at switch, CD4% decline >1 percentage point per month between switch date and preceding visit) were more likely to be switched, while taking a PI-based initial regimen was negatively associated with switch (aHR: 0.40; 95% CI: 0.17 to 0.91) (Table 4). Failure to initially attain viral load <400 copies per milliliter after starting ART was not associated with switch in univariable or multivariable analysis. (aHR: 1.02; 95% CI: 0.52 to 1.99).

DISCUSSION

Main Findings

This study reports in detail on confirmed VF and switching in children on ART in a large African multicenter

TABLE 3. Univariable and Multivariable Associations With Virologic Failure in All Children Commenced on ART (Cox-proportional Hazards Model Stratified by Site)

Failure Definition	2 Consecutive Unsuppressed Viral Loads With the Second Being >1,000 Copies/mL			
Characteristic at ART Initiation	Unadjusted HR (95% CI) n = 5485	*P*	Adjusted HR (95% CI), n = 3605	*P*
Age				
≥2 yrs	1	<0.001*	1	0.934*
1–2 yrs	1.37 (1.07 to 1.75)		1.02 (0.71 to 1.48)	
<1 year	1.83 (1.47 to 2.28)		1.07 (0.74 to 1.56)	
Female gender	0.88 (0.74 to 1.05)	0.16	0.92 (0.75 to 1.13)	0.442
Viral load > 1 million copies/mL	2.05 (1.63 to 2.58)	<0.001	1.67 (1.28 to 2.16)	<0.001
Severe immune suppression	1.48 (1.13 to 1.95)	0.004	1.25 (0.94 to 1.68)	0.131
WHO stage 3 or 4 (vs. 1 or 2)†	1.35 (1.06 to 1.73)	0.016	—	—
Weight-for-age *z* score < −3†	1.34 (1.06 to 1.69)	0.014	—	—
Third drug in regimen				
Efavirenz	1	—	1	—
Nevirapine	1.96 (1.37 to 2.80)	<0.001	1.77 (1.11 to 2.83)	0.016
Lopinavir/ RTV	1.36 (1.10 to 1.67)	0.004	1.07 (0.76 to 1.51)	0.701
Ritonavir alone	3.06 (2.31 to 4.04)	<0.001	2.39 (1.57 to 3.64)	<0.001
PMTCT exposure				
Unexposed/unknown	1	—	1	—
Exposed	1.64 (1.25 to 2.14)	<0.001	1.40 (1.02 to 1.92)	0.039
Year of ART initiation‡				
>2005	1	—	—	—
≤2005	0.83 (0.66 to 1.04)	0.1	—	—

*The *P* value was derived from Wald's test.
†Not included in multivariable model as missing information would have limited overall number of children that could be included.
‡Not included in multivariable model as $P > 0.1$ after adjustment for other variables in the model.
HR, hazard ratio.

TABLE 4. Univariable and Multivariable Associations With Switch to Second-Line Therapy in Children With at Least 6 Months Follow-Up After a Second Consecutive Unsuppressed Viral Load, With the Second Viral Load Being >1,000 Copies Per Milliliter (Cox-Proportional Hazards Model Stratified by Site)

Characteristic	Unadjusted HR (95% CI) n = 367	*P*	Adjusted HR (95% CI) n = 229	*P*
Age in years at ART initiation (per 1 year increase in age)	1.11 (1.05 to 1.16)	<0.001	1.03 (0.87 to 1.23)	0.698
Female gender	0.64 (0.44 to 0.92)	0.017	0.72 (0.42 to 1.25)	0.244
Years on treatment at time of failure (per 1 year duration on treatment)	1.38 (1.04 to 1.84)	0.025	1.37 (0.82 to 2.29)	0.229
Log_{10} viral load at failure (per 1 log increase)	1.43 (1.15 to 1.78)	0.002	1.55 (1.11 to 2.16)	0.01
Current* immunologic failure†	1.08 (0.67 to 1.75)	0.75	—	—
Current* CD4% <25	2.45 (1.56 to 3.84)	<0.001	1.94 (1.07 to 3.52)	0.029
Current CD4% decline > 1 unit/month‡	4.37 (2.14 to 8.92)	<0.001	6.44 (2.15 to 19.25)	0.001
Current* weight-for-age *z* score (per 1 unit increase in *z* score)	0.94 (0.78 to 1.13)	0.521	1.14 (0.90 to 1.43)	0.281
Current weight-for-age *z* score decline > 0.1 units/month‡	1.62 (0.64 to 4.11)	0.313	2.10 (0.58 to 7.58)	0.257
Viral load decline < 1 log_{10} since ART start†	0.88 (0.55 to 1.41)	0.596	—	—
PI-containing regimen	0.39 (0.25 to 0.60)	<0.001	0.40 (0.17 to 0.91)	0.03
Year of ART initiation†				
>2005	1	—	—	—
≤2005	1.10 (0.52 to 2.32)	0.803	—	—

Reasons for children having less than 6 months follow-up after failure (n = 156), were death (n = 5; 3%), loss to follow-up (n = 15; 10%), transfer out (n = 13; 8%) and failure occurring less than 6 months before database closure (n = 123; 79%).
HR, hazard ratio.
*Measurement taken at time of switch.
†Not include in multivariable model.
‡Difference between measurement taken at time of switch and preceding visit.

study where routine viral load monitoring was available. One in 5 children had met the analysis definition of confirmed VF by 3 years on ART. Baseline viral load >1 million copies per milliliter, use of either NVP, or RTV as a sole PI, and PMTCT exposure independently predicted failure. Less than half of children with ≥1 year of follow-up after failure were switched, with a median interval between failure and switch of 5.7 months. Across all sites, current poor immunologic and virologic status together with being on an NNRTI-based regimen favored switch.

Time to VF

Previous studies from Thailand and Uganda with all children on NNRTI-based regimens and failure defined using a single viral load measurement, reported similar proportions of children with VF at 12 months on ART as we report at 36 months using confirmed measurements.[5,6] Similarly, a recent cohort study found the frequency of consecutive viral load measurements >400 copies per milliliter among 116 children with follow-up ≥6 months to be 17%.[8] Nevertheless, the cumulative probability of a single elevated viral load measurement after 1 year on ART in our study (16%) is similar to the Thai and Ugandan studies. In contrast, prevalence of a single viral load measurement >400 copies per milliliter was 32% at a Tanzanian pediatric clinic, however, 12% of those with VF were on second-line.[9] Notwithstanding, our study differs from these with use of PI-based first-line therapy and possible differences in PMTCT exposure and adherence.

For those on NNRTI-based regimens, the confirmation of VF following adherence optimization, as reported in this study, is likely to identify patients who are truly failing with resistance to ≥1 drug in the regimen. For example, an adult study from South Africa showed that 86% of patients with confirmed viral load >1,000 copies per milliliter had therapy-limiting NNRTI mutations.[27] Among children with VF in the Thai study, 89% and 97% had major NRTI and NNRTI resistance mutations, respectively. We had no access to resistance testing for children failing therapy, and the prevalence of resistance among children on PI-based regimens with confirmed VF in our context remains unknown.

Comparisons with rich countries are difficult due to differences in age at ART commencement, previous monotherapy or dual therapy, follow-up duration, and first-line regimens. The United Kingdom Collaborative HIV Pediatric Study reported 32% of 595 children having VF after a median follow-up of 3 years, whereas a Dutch cohort of 39 children on nelfinavir-based ART reported 74% VF-free survival after 48 weeks.[28,29]

First-Line Regimen Choice

The association between NVP-containing regimens and VF concurs with findings from previous pediatric and adult studies.[5,6,30,31] It has been suggested that NVP may be underdosed in children taking split adult fixed-dose combination tablets, however, in South Africa, NVP is administered to children as a single drug in syrup/tablet form.[5,6] Children may harbor resistance from unrecorded exposure to sdNVP, and subsequent NVP-based ART would be expected to result in poor virologic outcomes.[32,33] Although the majority of sdNVP-exposed children in this cohort would have commenced PI-based regimens, it is likely that some initiated NNRTI-based regimens due to site variation in regimen use

before national guidelines recommendations. This is supported by both the finding of an association between PMTCT exposure and subsequent failure, despite PMTCT underascertainment, and attenuation of this effect when those without virologic response to ART were excluded. This attenuation is expected as children with NVP resistance would most likely be virologic nonresponders.

Despite our inability to adjust for potential confounding by concomitant tuberculosis and other confounding by indication, our findings suggest that RTV as the sole PI is indeed associated with failure. RTV is unpleasant tasting, associated with poor adherence, and results in a greater accumulation of major PI resistance mutations in comparison with LPV/r.[34,35] However, as RTV use would have been more common in children with tuberculosis, we cannot exclude that worse outcomes may have been due to tuberculosis itself or the increased medication burden of ART combined with antituberculous therapy.

Switching to Second-Line

This study reflects clinical practice in a setting with viral load monitoring but no supporting national or WHO guidelines regarding management of children with VF. This is reflected in the low proportion of children switched after failure, and the delay between VF and switch. Heterogeneity in switching practice was also seen in the Collaborative HIV Pediatric Study with nearly half of children with VF being switched before the date of first viral load >1000 copies per milliliter but an equal proportion on first line ≥6 months thereafter.[28] In our study, service factors may contribute to the delay; clinical appointments are often 3-monthly with results only available for decision-making at subsequent appointments.

Nevertheless, less than half of children with confirmed VF for ≥1 year were switched, and those who were switched were on a failing regimen for a median of 10 months after the first elevated viral load measurement. In this study, factors other than VF were associated with being switched, including initial regimen, disease severity and progressive immunological decline.

Reluctance to switch a young child failing therapy without thorough assessment of adherence is reasonable in the context of access only to unpleasant second-line regimens, with no third-line/salvage therapy. In this respect, reduced switching of children on PI-based regimens is consistent with knowledge that viral escape is more likely due to poor adherence than resistance.[34] Nevertheless, poor access to a wider range of second-line drugs, particularly for children failing first-line PI-based regimens after sdNVP exposure, may result in an understandable reluctance to switch children to a drug to which their virus may be resistant.

If the intention of treatment guidelines is to avoid prolonged viremia, this study suggests the need for more intensive monitoring and adherence interventions soon after a single elevated viral load. The PENPACT1 trial recently reported similar outcomes overall for children switched at viral load measurements of 1000 or 30,000 copies per milliliter, however, highlighted the importance of adherence interventions after initial elevated viral load measures.[36,37] In addition, children on NNRTI-based therapy switched at 30,000 copies per milliliter accumulated more NRTI-resistant mutations compared with those switched at 1000 copies per milliliter, suggesting that switching guidelines should be tailored according to regimen.[36,37] In large programs, viral load monitoring could additionally be used to manage patient load by stratifying risk. More clinical and adherence input could be given to unsuppressed patients although those with sustained virologic suppression could be managed less intensively.[7,38]

Strengths and Limitations

This is a large combined cohort of children across many sites providing different levels of care. In addition, viral load measurements were available for >75% of children in care at each 6-monthly duration, and it was possible to use as an outcome confirmed VF rather than a single measure. The large number of infants and inclusion of a PI in first line enabled us to examine the effect on virologic outcome of RTV as the sole PI and LPV/r in comparison to NVP or EFV as components of first-line regimens.

The size of the cohort resulted in a relatively large absolute number of failures and switches, permitting investigation of switching practice.

Despite the study size and the general application of the public health approach to ART provision, the study cohorts, being relatively well resourced and urban, may not be representative of all sites across the region or even South Africa.

Data was collected in the context of routine care in busy clinics. There is limited data on key possible predictors of VF such as tuberculosis coinfection, adherence and PMTCT, and on clinical events. Missing data on other variables limited the range of variables and number of children that could be included in multivariable models. Tuberculosis coinfection not only affects first-line regimen choice, but may impact on virologic outcomes directly or through drug–drug interactions or reduced adherence. We could not explore the extent to which our observed associations with failure were mediated through poor adherence, due to limited data. PMTCT exposure data was only recorded for 40% of children. Furthermore, exact PMTCT regimens were not recorded, so the effect of different regimens could not be examined. The effect of severe clinical disease at ART initiation on VF may have been reduced by combining stage 3 and 4 disease. Due to lack of detailed clinical event data and confounding by indication (with sicker children being preferentially switched), we were unable to determine the clinical consequences of delayed switching.

CONCLUSIONS

This study demonstrates the probability of VF in children on ART in South Africa at 3 years to be nearly 20%. The time between failure and switch and low proportion of children switched to second-line in this and other studies supports use of clearer definitions of VF and clinical practice guidelines for managing children with unsuppressed viral load tailored to starting regimen. In addition, access to second-line drugs for PMTCT exposed children failing PI-based ART is important for better pediatric HIV care in the countries where the majority of HIV-infected children reside.

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APPENDIX: IEDEA SOUTHERN AFRICA STEERING GROUP

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2.5 Accuracy of immunological criteria for identifying virological failure in children on antiretroviral therapy – The IeDEA Southern Africa Collaboration

2.6 The role of targeted viral load testing in diagnosing virological failure in children on antiretroviral therapy with immunological failure

Overview of papers

These papers used data from South African IeDEA-SA sites that had access to both CD4 and virological monitoring at least six monthly for the duration of the period of analysis. The first paper describes the poor diagnostic accuracy of WHO and USA Department of Health and Human Services (DHHS) Guidelines immunological failure criteria for identifying children with confirmed VF. The second paper analyses the improvement in positive predictive value (PPV) when a single targeted viral load (TVL) measurement is performed in children identified as having immunological failure (IF).

Contribution to the thesis and novelty

Together these papers address the third objective of the thesis, examining the measurement of treatment success in settings without access to routine HIV-RNA monitoring. Both studies are the biggest to compare HIV-RNA and CD4 measures and the only studies to do this continuously for up to three years with failure diagnosis based on a confirmed viral load. The first paper demonstrates that all IF criteria have low sensitivity and PPV for identifying children with confirmed VF, supporting results of previously published smaller studies. The second paper is the only published study to evaluate TVL in children and shows that a TVL strategy increases PPV of DHHS and WHO IF criteria for VF to >80%.

Role of the candidate

The candidate was responsible for all data management to generate the IeDEA paediatric data sets for these analyses. She was solely responsible for the analyses. The first analysis was presented at the 2nd International Workshop on HIV Pediatrics in Vienna in 2010 and the second at the South African AIDS Conference in Durban in 2011. The candidate drafted both manuscripts, incorporated input from co-authors and was responsible for finalising and submitting the final versions of the manuscript for publication.

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Accuracy of immunological criteria for identifying virological failure in children on antiretroviral therapy – The IeDEA Southern Africa Collaboration

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Summary

OBJECTIVES To determine the diagnostic accuracy of World Health Organization (WHO) 2010 and 2006 as well as United States Department of Health and Human Services (DHHS) 2008 definitions of immunological failure for identifying virological failure (VF) in children on antiretroviral therapy (ART).

METHODS Analysis of data from children (<16 years at ART initiation) at South African ART sites at which CD4 count/per cent and HIV-RNA monitoring are performed 6-monthly. Incomplete virological suppression (IVS) was defined as failure to achieve ≥1 HIV-RNA ≤400 copies/ml between 6 and 15 months on ART and viral rebound (VR) as confirmed HIV-RNA ≥5000 copies/ml in a child on ART for ≥18 months who had achieved suppression during the first year on treatment.

RESULTS Among 3115 children [median (interquartile range) age 48 (20–84) months at ART initiation] on treatment for ≥1 year, sensitivity of immunological criteria for IVS was 10%, 6% and 26% for WHO 2006, WHO 2010 and DHHS 2008 criteria, respectively. The corresponding positive predictive values (PPV) were 31%, 20% and 20%. Diagnostic accuracy for VR was determined in 2513 children with ≥18 months of follow-up and virological suppression during the first year on ART with sensitivity of 5% (WHO 2006/2010) and 27% (DHHS 2008). PPV results were 42% (WHO 2010), 43% (WHO 2006) and 20% (DHHS 2008).

CONCLUSION Current immunological criteria are unable to correctly identify children failing ART virologically. Improved access to viral load testing is needed to reliably identify VF in children.

keywords children, antiretroviral therapy, immunological criteria, sensitivity, specificity, virological failure

Introduction

Poor access to viral load testing in resource-limited settings results in reliance on immunological criteria to identify treatment failure in patients on antiretroviral therapy (ART). Studies in adults have shown limited value of immunological criteria to detect virological failure (VF) (Badri *et al.* 2008; Mee *et al.* 2008; Keiser *et al.* 2009). While low sensitivity of immunological criteria for identifying VF could result in delayed switching to second-line treatment with accumulation of resistance mutations, low positive predictive value (PPV) may incorrectly identify patients as needing second-line treatment when they are virologically suppressed. The few paediatric studies of

diagnostic accuracy of immunological criteria for VF are limited by small cohort size and/or VF definition based on single elevated HIV-RNA measurements (Jittamala *et al.* 2009; Emmett *et al.* 2010; Ruel *et al.* 2010). We analysed data from routine paediatric ART clinics to determine the diagnostic accuracy of WHO (2006, 2010) and United States Department of Health and Human Services (DHHS) 2008 (National Institutes of Health 2008) criteria for immunological failure for identifying (i) incomplete virological suppression (IVS) during the first year on ART, and (ii) confirmed viral rebound (VR).

Methods

Data were collected prospectively from ART-naïve children (<16 years at ART start) initiating ≥3 antiretrovirals at South African sites participating in IeDEA–Southern Africa (IeDEA-SA, see http://www.iedea-sa.org), all of which had CD4 and HIV-RNA measurements performed 6-monthly. The characteristics of these sites have been described previously (Davies *et al.* 2009). Each site has institutional ethical approval to contribute data to IeDEA analyses.

HIV-RNA was measured using Amplicor 1.5 (Roche Diagnostics) or NucliSens EasyQ assays (bioMerieux), with good comparability (Stevens *et al.* 2005). CD4 measurements were performed using standard dual platform flow cytometry or the single platform PanLeucogated method (Glencross *et al.* 2008). We defined IVS as failure to achieve ≥1 HIV-RNA ≤400 copies/ml between 6 and 15 months on ART and VR as confirmed HIV-RNA ≥5000 copies/ml in a child on ART for ≥18 months whose HIV-RNA had suppressed during the first year on treatment. We examined the following immunological criteria: WHO 2010: No definition for children <2 years; CD4% <10% or CD4 <200 cells/mm^3 (age 2–4 years); CD4 <100 cells/mm^3 (age ≥5 years) (WHO 2010). WHO 2006: No definition for children <1 year; CD4% <15% (age 1–2 years); CD4% <10% (age 3–4 years); CD4 <100 cells/mm^3 (age ≥5 years) (WHO 2006). DHHS: During first year on ART: <5 percentage point CD4% increase from baseline (CD4% <15 and age <5 years at baseline) or <50 cells/mm^3 CD4 increase from baseline (CD4 <200 cells/mm^3 and age ≥5 years at baseline); decline of CD4% by 5 percentage points from previous value, confirmed at subsequent measurement (<365 days after first low value) (any age); return of CD4 count ≤baseline value (age ≥5 years at baseline) (National Institutes of Health 2008).

For IVS, we assessed the diagnostic accuracy of *never* achieving a CD4 above the immunological thresholds between 6 and 15 months on ART for identifying a child who *never* had HIV-RNA ≤400 copies/ml during the same period. Only children followed up for ≥1 year with ≥1 HIV-RNA measurement between 6 and 15 months were included. For VR, CD4 and HIV-RNA measurements were carried forward for up to 3 months where tests were performed asynchronously. For each unique paired CD4 and HIV-RNA measurement, we determined the diagnostic value of CD4-based criteria for identifying VR, using robust standard errors to account for multiple measures per patient. Immunological results for which there was still no concurrent virological diagnosis after carrying forward results were not evaluated. Further, the last immunological result before the end of follow-up/database closure was excluded to ensure that there was sufficient follow-up for a confirmatory low viral load measurement to have been performed. Separate sensitivity analyses were performed requiring either consecutive (within 365 days) CD4 measurements meeting immunological criteria or using an HIV-RNA threshold of 1000 copies/ml to define confirmed VR.

Results

Of 3640 children with ≥1 year of follow-up, 3115 (86%) had ≥1 HIV-RNA measurement between 6 and 15 months on ART. At ART initiation, median [interquartile range (IQR)] age was 48 (20–84) months. Most children were severely ill at ART initiation: WHO-defined severe immune suppression was present in 81% of 2911 children with baseline CD4 measures recorded, and 68% of 2294 children with WHO Clinical Stage data had Stage 3/4 disease (WHO 2006). In keeping with South African guidelines recommending protease inhibitor- (PI-) based first-line therapy in children <3 years old (National Department of Health South Africa 2005), 35% of children were on PI-based first-line treatment with non-nucleoside reverse transcriptase-based therapy in the remainder. IVS occurred in 12.6% of children and sensitivity of immunological criteria for identifying IVS ranged from 6% (WHO 2010) to 26% (DHHS) and PPV from 20% (WHO 2010 and DHHS) to 31% (WHO 2006) (Table 1a).

The accuracy of immunological criteria for identifying VR was assessed in 2513 children with at least 18 months follow-up on ART whose HIV-RNA had suppressed during the first year on treatment. The cumulative probability of VR in the following 2 years (by 42 months since ART start) was 5.5% [95% confidence interval (CI): 4.2–7.1]. Sensitivity of immunological criteria for identifying VR ranged from 5% (WHO 2006/2010) to 27% (DHHS) and PPV from 20% (DHHS) to 43% (WHO 2006) (Table 1b). For diagnosing both IVS and VR, requiring consecutive CD4 counts to meet immunological

Table 1 Diagnostic value of immunological criteria for identifying children (a) with incomplete virological suppression during first year on ART and (b) with viral rebound

	Comparison of immunological failure diagnosis (based on highest CD4 between 6 and 15 months on ART) with failure of viral suppression in same period			Comparison of immunological failure diagnosis (based on highest CD4 between 6 and 15 months on ART and confirmed on a subsequent measurement) with failure of viral suppression in same period		
(a)	WHO 2006*	WHO 2010†	USA	WHO 2006*	WHO 2010†	USA
Number of children (%)	90/2714 (3.3)	61/2380 (2.6)	355/2585 (13.7)	13/2502 (0.5)	9/2217 (0.4)	72/2277 (3.2)
Number of children with paired data‡	2581	2256	2470	2405	2126	2190
Sensitivity (%)	10 (7–14)	6 (3–10)	26 (21–31)	2 (0–4)	2 (0–4)	9 (5–12)
Specificity (%)	97 (97–98)	98 (97–98)	87 (86–89)	99 (99–100)	99 (99–100)	97 (97–98)
PPV (%)	31 (22–41)	20 (10–30)	20 (16–24)	38 (8–69)	33 (0–72)	27 (16–38)
NPV (%)	90 (89–91)	92 (91–93)	91 (89–92)	90 (89–91)	92 (91–93)	90 (89–92)
Number of true positives	28	12	69	5	3	19
Number of true negatives	2242	2017	1928	2151	1945	1916
Number of false negatives	250	179	197	241	172	204
Number of false positives	61	48	276	8	6	51
LR+	3.80	2.70	2.07	5.49	5.57	3.29
LR−	0.92	0.95	0.85	0.98	0.99	0.94
Area under ROC curve	0.537	0.520	0.567	0.508	0.507	0.530

ART, antiretroviral therapy; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio of a positive test; LR−, likelihood ratio of a negative test; ROC, receiver operating characteristic.
*Only determined for children >12 months of age.
†Only determined for children >24 months of age.
‡Number of children with paired data (both CD4 and HIV-RNA measures available and CD4 criteria evaluable in terms of immunological criteria) differs for different definitions because of different age and data requirements for each definition.

	Comparison of immunological failure diagnosis (based on single CD4 measure meeting criteria) with confirmed HIV-RNA >5000 copies/ml			Comparison of immunological failure diagnosis (based on consecutive CD4 measures meeting criteria) with confirmed HIV-RNA >5000 copies/ml		
(b)	WHO 2006	WHO 2010*	USA	WHO 2006	WHO 2010*	USA
Cumulative probability by 2 years	2.2% (1.5–3.2)	2.3% (1.5–3.3)	28.1% (25.2–31.3)	0.4% (0.2–1.0)	0.3% (0.1–0.9)	10.4% (8.6–12.6)
Number of evaluable pairs of data†	2499	2593	2191	2395	2507	2110
Sensitivity (%)	5 (2–9)	5 (2–9)	27 (19–35)	2 (0–5)	2 (0–4)	13 (6–21)
Specificity (%)	99 (99–100)	99 (99–100)	88 (86–90)	100 (99–100)	100 (99–100)	95 (94–96)
PPV (%)	43 (23–63)	42 (22–61)	20 (13–26)	50 (19–81)	44 (14–75)	21 (10–32)
NPV (%)	91 (89–93)	91 (89–93)	92 (90–94)	91 (89–93)	91 (89–93)	91 (89–93)
Number of true positives	13	13	58	5	4	26
Number of true negatives	2245	2327	1740	2168	2269	1816
Number of false negatives	224	235	157	217	229	172
Number of false positives	17	18	236	5	5	96
LR+	7.30	6.83	2.26	9.79	7.81	2.62
LR−	0.95	0.95	0.83	0.98	0.98	0.91
Area under ROC curve	0.524	0.522	0.575	0.510	0.508	0.541

PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio of a positive test; LR−, likelihood ratio of a negative test; ROC, receiver operating characteristic.
*Only determined for children >24 months of age.
†Paired data created from carrying forward asynchronously measured CD4 and HIV-RNA results for up to 3 months; Number of children with paired data differs for different definitions because of different age and data requirements for each definition.

criteria increased PPV only slightly at the expense of sensitivity, without any improvement in the receiver operating characteristic curve (Table 1). For VR, lowering the VR threshold to 1000 copies/ml and using confirmed CD4 values to define immunological criteria yielded sensitivity (95% CI) of 2% (0–5%) (WHO 2006); 2% (0–4%) (WHO 2010) and 14% (8–19%) (DHHS); and PPV (95% CI) of 90% (72–100%) (WHO 2006); 89% (68–100%) (WHO 2010) and 38% (26–50%) (DHHS).

Discussion

In this large longitudinal study, we found that sensitivity and PPV were low for identifying VF using WHO and DHHS immunological criteria. For example, using confirmed HIV-RNA ≥5000 copies/ml after initial virological suppression to define VR, sensitivity was only 4% using either WHO 2006 or 2010 criteria. Fewer than half of children meeting WHO 2006/2010 criteria would have HIV-RNA ≥5000 copies/ml.

These results concur with those of previous small studies from resource-limited settings. Among 116 children in Uganda, 20 (17%) had sustained viraemia (≥400 copies/ml) beyond 24 weeks on ART (Ruel *et al.* 2010). Only two of these ever met WHO 2006 immunological criteria and did so after >550 days of viraemia, while none met WHO 2010 criteria (Ruel *et al.* 2010). Similarly, in a cross-sectional study of 206 children in Tanzania on ART for a median duration of 2.4 years, 32% had a single HIV-RNA ≥400 copies/ml (Emmett *et al.* 2010). WHO 2006 clinical and immunological failure criteria combined had a PPV of 100% but identified only 3.5% of children with HIV-RNA ≥400 copies/ml (Emmett *et al.* 2010). In Thailand, the sensitivity and PPV of DHHS immunological criteria for identifying children with a single HIV-RNA >1000 copies/ml were 15% and 16%, respectively (Jittamala *et al.* 2009).

The poor sensitivity of immunological criteria for identifying VF is disappointing; however, perhaps, an even greater concern is preventing the incorrect diagnosis of treatment failure in a virologically suppressed child, with unnecessary switch to second-line treatment, hence the importance of PPV. While PPV reached 89% for identifying VR ≥1000 copies/ml using a confirmed CD4 value meeting WHO 2010 criteria, given that the WHO 2010 guidelines HIV-RNA threshold for switching to second-line is 5000 copies/ml, in most instances the number of false positives using immunological criteria is unacceptably high. Further, absence of immunological failure on ART provides no assurance that a child is virologically suppressed and not accumulating resistance mutations, and even high CD4 thresholds (e.g. DHHS criteria) have low sensitivity for VF (PENPACT1 Study Team 2011). Improved access to HIV-RNA monitoring both to assess adherence and identify VF is therefore needed (Wilson *et al.* 2009; Ford & Calmy 2010).

There are several limitations to this analysis of routinely collected data. Missing baseline CD4 values limited the evaluation of DHHS criteria. Baseline CD4 values are often unavailable to clinicians if children initiate ART on clinical criteria, records are lost or a child changes treatment site after ART initiation, highlighting the value of simple criteria using current or recent measurements. The accuracy of WHO 2006 and 2010 criteria could not be evaluated in children <1 and <2 years old, respectively. Work-up bias may occur if either the reference (HIV-RNA) or index (CD4) tests are not applied consistently (Whiting *et al.* 2004). In particular, rigorous confirmation of low CD4 values is seldom performed in South Africa, owing to access to HIV-RNA measurements to diagnose treatment failure. Exclusion of intercurrent illness as a cause of low CD4, as advised in WHO guidelines (WHO 2010), was not possible because of limited data on episodes of clinical illness. Immunological criteria may have performed better if only low CD4 counts not explained by intercurrent illness had been considered. PPV is dependent on the VF incidence in different programs; however, the incidence in this cohort was similar to that of other studies (Kamya *et al.* 2007; Jittamala *et al.* 2009; Davies *et al.* 2011).

In summary, our results suggest that current immunological criteria are unable to correctly identify children failing ART virologically. Improved access to viral load testing appears to be the only feasible approach at this stage for reliably identifying VF in children on ART. There are several existing technologies for the measurement of viral load (Stevens & Marshall 2010), and expanded access should be supported by governments and donors.

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The role of targeted viral load testing in diagnosing virological failure in children on antiretroviral therapy with immunological failure

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Abstract

OBJECTIVES To determine the improvement in positive predictive value of immunological failure criteria for identifying virological failure in HIV-infected children on antiretroviral therapy (ART) when a single targeted viral load measurement is performed in children identified as having immunological failure.

METHODS Analysis of data from children (<16 years at ART initiation) at South African ART sites at which CD4 count/per cent and HIV-RNA monitoring are performed 6-monthly. Immunological failure was defined according to both WHO 2010 and United States Department of Health and Human Services (DHHS) 2008 criteria. Confirmed virological failure was defined as HIV-RNA >5000 copies/ml on two consecutive occasions <365 days apart in a child on ART for ≥18 months.

RESULTS Among 2798 children on ART for ≥18 months [median (IQR) age 50 (21–84) months at ART initiation], the cumulative probability of confirmed virological failure by 42 months on ART was 6.3%. Using targeted viral load after meeting DHHS immunological failure criteria rather than DHHS immunological failure criteria alone increased positive predictive value from 28% to 82%. Targeted viral load improved the positive predictive value of WHO 2010 criteria for identifying confirmed virological failure from 49% to 82%.

CONCLUSION The addition of a single viral load measurement in children identified as failing immunologically will prevent most switches to second-line treatment in virologically suppressed children.

keywords HIV, virological failure, children, antiretroviral therapy, monitoring, immunological failure

Introduction

In many resource-limited settings, access to HIV-RNA measurement is limited and clinicians rely on clinical and immunological criteria to identify children failing first-line antiretroviral therapy (ART). These criteria have poor diagnostic accuracy for virological failure, with both low sensitivity and positive predictive value (PPV; Jittamala *et al.* 2009; Ruel *et al.* 2010; Davies *et al.* 2011). Low PPV means that children may be inappropriately switched to limited and expensive second-line ART, when they are still virologically suppressed. Confirming treatment failure with a single elevated targeted HIV-RNA measurement once immunological failure criteria are met [targeted viral load (TVL) approach], together with a thorough

*The members of IeDEA Southern Africa Collaboration are given in Appendix.

assessment of adherence, may prevent switches to second-line when the virus is likely to still be sensitive to the first-line regimen. This approach is recommended in WHO 2010 pediatric treatment guidelines (Rewari *et al.* 2010, WHO 2010). For example, inappropriate switches to second-line of adults who had TVL performed were far less common than of those with CD4 monitoring only (12.4% *vs.* 46.9%; Sigaloff *et al.* 2011).

Different CD4 thresholds have been used to define immunological failure (IF). For example, the United States Department of Health and Human Services (DHHS) 2008 guidelines defined children as failing immunologically if they experienced any of: a confirmed decline of CD4% by five percentage points from the previous value or a return of CD4 count to below the baseline value in child aged at least 5 years at baseline (National Institutes of Health, 2008). The WHO 2010 guidelines consider a child to be failing immunologically if CD4% or CD4 count declines to <10% or 200 cells/mm^3, respectively (children aged 2–4 years), or CD4 count declines to <100 cells/mm^3 (children aged ≥5 years). No definition of IF is provided for children <2 years of age (WHO 2010). We have previously shown that the sensitivity of the DHHS 2008 IF definition [27%; 95% confidence interval (CI): 19–35%] was greater than that of WHO 2010 definition (5%; 95% CI: 2–9%) for identifying children with confirmed virological rebound (Davies *et al.* 2011; Note: Confirmed virological rebound was defined as HIV-RNA >5000 copies/ml on two consecutive occasions <365 days apart in a child on ART for ≥18 months who achieved suppression during the first year on ART). However, PPV was low for both DHHS (20%; 95% CI: 13–26%) and WHO 2010 (42%; 95% CI: 22–62%) criteria. While these results underline the value of routine HIV-RNA monitoring, access is likely to remain limited in the short term in many settings because of financial and logistical constraints (Sigaloff *et al.* 2011). Therefore, we aimed to use data from children receiving ART at South African IeDEA-Southern Africa (IeDEA-SA) sites, all of which had access to at least 6-monthly CD4 and HIV-RNA monitoring, to determine to what extent PPV for identifying virological failure improves when adding TVL to either DHHS or WHO 2010 IF criteria.

Methods

Data were collected prospectively from ART-naïve children (<16 years at ART start) initiating ≥3 antiretroviral drugs at South African sites participating in IeDEA-SA (http://www.iedea-sa.org). Site characteristics have been described previously (Davies *et al.* 2009). Each site has institutional ethical approval to contribute data to IeDEA analyses. HIV-RNA was measured using Amplicor 1.5 (Roche Diagnostics) or NucliSens EasyQ assays (bioMerieux), with good comparability (Stevens *et al.* 2005). CD4 measurements were performed using standard dual platform flow cytometry or the single platform PanLeucogated method (Glencross *et al.* 2008).

Confirmed virological failure (CVF) was defined as HIV-RNA >5000 copies/ml on two consecutive occasions <365 days apart in a child who had been on treatment for at least 18 months irrespective of whether suppression to <400 copies/ml was achieved in the first year on treatment. IF criteria were as follows: DHHS: a decline of CD4% by five percentage points from the previous value, confirmed at a subsequent measurement within 365 days after the first low value (applicable to a child of any age) or a return of CD4 count to below the baseline value in child aged at least 5 years at baseline (National Institutes of Health, 2008). WHO (2010): no definition for children <2 years; CD4% <10% or CD4 <200 cells/mm^3 (age 2–4 years); CD4 <100 cells/mm^3 (age ≥5 years). For each of these IF criteria, children were further considered to meet TVL failure criteria if they met the respective IF criteria and the next HIV-RNA measurement (within 4 months of meeting IF criteria) was >5000 copies/ml. CD4 results for which there was no available HIV-RNA measurement within 4 months, which was required to assess TVL, were excluded from the analysis (1% and <1% of measurements for DHHS 2008 and WHO 2010 criteria, respectively).

For all failure diagnoses (IF, TVL or CVF), measurements had to be taken during a period when the child was on treatment and not during a treatment interruption. Where tests were performed asynchronously, IF, TVL and CVF diagnoses were carried forward for up to 3 months. We compared each unique paired TVL and CVF diagnosis to determine diagnostic accuracy, using robust standard errors to account for multiple measures per patient. TVL results for which there was no concurrent CVF diagnosis after carrying forward results were not evaluated. The last TVL result before the end of follow-up was excluded to ensure that sufficient follow-up for a confirmatory low viral load measurement had been performed. All analyses were performed using STATA 11 (Stata Corporation, College Station, TX, USA).

Results

Data from 2798 children on ART for ≥18 months were included. Characteristics at ART initiation were as follows: median (interquartile range) age 50 (21–84) months; 48% female; 64% WHO Clinical Stage 3 or 4 and 79% WHO-defined severe immune suppression. One-third of children started a protease inhibitor-based first-line regimen. The cumulative probability of CVF by 42 months on ART was

6.3%. Using TVL after meeting DHHS IF criteria rather than DHHS IF criteria alone increased PPV from 28% to 82% and the likelihood ratio of a positive test from 2.08 to 23.89, respectively (Table 1). Among the 19 TVL-diagnosed false positive cases, 8 (42%) had two HIV-RNA measurements >400 copies/ml but only one >5000 copies/ml, and 11 (58%) had a single elevated HIV-RNA with resuppression at subsequent measurement.

Using TVL after meeting WHO IF criteria rather than WHO IF criteria alone increased PPV from 49% to 82% and the likelihood ratio of a positive test from 5.41 to 25.98, respectively (Table 1). Among the four TVL-diagnosed false positive cases, three (75%) had two HIV-RNA measurements >400 copies/ml but only one >5000 copies/ml, and one (25%) had a single elevated HIV-RNA with resuppression at subsequent measurement.

Discussion

These results illustrate that although even the most sensitive immunological criteria detect only a quarter of cases of virological failure, the addition of TVL to these criteria raises PPV and could reduce the number of switches to second-line treatment in virologically suppressed children. More than 80% of children considered to be failing therapy according to either DHHS or WHO IF criteria together with TVL would also meet the criteria for CVF.

Nevertheless, TVL results in a small but important number of false positive diagnoses as a proportion of children resuppress after a single elevated HIV-RNA measurement. Although children were not considered to be failing therapy according to any definition if measurements were taken during a documented treatment interruption, we did not have detailed adherence data. It is possible that these measurements may have been taken during adherence lapses. Because these data come from programs with routine HIV-RNA monitoring, the elevated HIV-RNA measurement may have actually facilitated identification of poor adherence, prompting counselling and intervention with subsequent resuppression (Wilson *et al.* 2009). This adds to the evidence in adults supporting HIV-RNA measurement as a tool to discriminate between poor adherence and therapeutic failure (Calmy *et al.* 2007; Orrell *et al.* 2007). Routine HIV-RNA monitoring also allows early accurate identification of virological failure and consequent switching to second-line, thus preventing accumulation of resistance mutations, which is not possible with a more limited TVL approach (Wilson *et al.* 2009; Sigaloff *et al.* 2011). Indeed, modelling studies in children suggest that annual HIV-RNA monitoring after an initial screen 6 months after ART start would result in a 77% reduction in time spent with virological failure compared with no HIV-RNA monitoring (Schneider *et al.* 2011).

Strengths of this study include the large cohort across many sites in South Africa with routine access to both CD4

Table 1 Diagnostic accuracy of DHHS and WHO immunological failure (IF) criteria alone and DHHS and WHO IF criteria with targeted viral load monitoring (TVL) for identifying children with confirmed virological failure (CVF)

	DHHS IF criteria met	DHHS IF criteria met and next HIV-RNA ≥5000 copies/ml	WHO IF criteria met	WHO IF criteria met and next HIV-RNA ≥5000 copies/ml
Cumulative probability by 2 years (95% CI)	28.8% (26.0–31.8)	5.8% (4.6–7.3)	2.4% (1.7–3.4)	1.2% (0.8–2.0)
Number of evaluable pairs of data*	2524	2480	2945	2906
Sensitivity (%) (95% CI)	24 (19–29)	22 (17–27)	4 (2–6)	4 (2–6)
Specificity (%) (95% CI)	88 (87–90)	99 (99–100)	99 (99–100)	100 (100–100)
PPV (%) (95% CI)	28 (22–35)	82 (74–90)	49 (31–66)	82 (65–99)
NPV (%) (95% CI)	86 (84–88)	87 (85–89)	86 (83–88)	86 (84–88)
Number true positives	98	86	18	18
Number true negatives	1873	2066	2487	2473
Number false negatives	306	309	421	411
Number false positives	247	19	19	4
LR+	2.08	23.89	5.41	25.98
LR−	0.85	0.79	0.97	0.96
Area under ROC curve	0.563	0.604	0.517	0.520

*Evaluable pairs refers to each unique occasion where a diagnosis according to either IF or IF + TVL criteria can be compared with the CVF diagnosis. Number of evaluable pairs differs for different definitions because of different data requirements for each definition.

and HIV-RNA measurement, hence the large number of TVL and CVF results available for comparison. Limitations of these routinely collected data include missing baseline CD4 values in some children, which limited evaluation of DHHS criteria, work-up bias that may occur if either the reference (HIV-RNA) or index (CD4 with single HIV-RNA) tests are not applied consistently (Whiting *et al.* 2004) or when people switch to a second-line regimen before immunological failure occurs. The study was further limited by lack of data with respect to intercurrent illnesses that should be excluded before considering a low CD4 count to be indicative of immunological failure (WHO 2010).

We conclude that the addition of targeted viral load to CD4 monitoring will prevent most switches to second-line therapy in virologically suppressed children. This is particularly important to avoid exhausting the limited drug options for children facing lifelong therapy. Our previous study demonstrated the low sensitivity of immunological criteria for identifying virological failure (Davies *et al.* 2011), and TVL should not replace routine HIV-RNA monitoring in settings such as South Africa where it is available or easily achievable. Rather, the introduction of TVL may be a first step towards increasing access to routine viral load monitoring where this is currently unavailable.

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Appendix

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2.7 Temporal trends in the characteristics of children at antiretroviral therapy initiation in Southern Africa: The International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration

Paper overview

This paper describes temporal trends in the number and characteristics of >30,000 children that initiated ART from 2005-2010 at all IeDEA-SA sites.

Contribution to the thesis and novelty

This paper addresses the fourth objective of the thesis. It is the largest analysis of temporal trends in patient characteristics at ART initiation based on individualized data. It is the only study including a range of settings in more than one country. The number of children included is nearly 10% of all children estimated to have been receiving ART in eastern and southern Africa by the end of 2010. The study demonstrates that there have been significant increases in the number of children starting treatment and improvement in disease severity of patients at ART initiation. There have been increases in the proportion of both infants and older children (≥ 10 years of age) in later years. The study found that even by the end of 2010, most children still initiate ART with severe disease.

Role of the candidate

The candidate was responsible for all data management to generate the IeDEA paediatric data sets for these analyses. She was solely responsible for the analysis. The candidate drafted the manuscript, incorporated input from co-authors and was responsible for finalising and submitting the final version of the manuscript for publication.

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TITLE: Temporal trends in the characteristics of children at antiretroviral therapy initiation in Southern Africa: The IeDEA-SA Collaboration

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SHORT TITLE: Characteristics at ART initiation in children

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ABSTRACT

Background: Since 2005, increasing numbers of children have started antiretroviral therapy (ART) in sub-Saharan Africa and, in recent years, WHO and country guidelines for ART initiation have recommended ART initiation for all infants and very young children, and at higher CD4 thresholds for older children. We examined temporal changes in patient and regimen characteristics at ART start using data from 12 cohorts in 4 countries participating in the IeDEA-SA collaboration.

Methods: Data from 30,300 ART-naïve children aged <16 years at ART initiation who started therapy between 2005 and 2010 were analysed. We examined changes in median values (continuous variables) using the Cuzick's test for trend over time. We also examined changes in the proportions of patients with particular disease severity (expressed as a binary variable e.g. WHO Stage III/IV vs I/II) using logistic regression.

Results: Between 2005 and 2010 the number of children starting ART each year increased and median age declined from 63 months (2006) to 56 months (2010). Both the proportion of children <1 year and ≥10 years of age increased from 12-19% and 18-22% respectively. Children had less severe disease at ART initiation in later years with significant declines in the percentage with severe immunosuppression (81–63%), WHO Stage III/IV disease (75-62%), severe anemia (12-7%) and weight-for-age z-score <-3 (31-28%). Similar results were seen when restricting to infants with significant declines in the proportion with severe immunodeficiency (98-82%) and Stage III/IV disease (81-63%). First-line regimen use followed country guidelines.

Conclusion: Between 2005 and 2010 increasing numbers of children have initiated ART with a decline in disease severity at start of therapy. However, even in 2010, a substantial number of infants and children started ART with advanced disease.

Introduction

The estimated number of children receiving antiretroviral therapy (ART) in southern and eastern Africa has increased several-fold from <50,000 in 2005 to 337,200 by the end of December 2010, corresponding to a coverage of 26% of those eligible for ART.[1] In addition, WHO 2010 guidelines advocate immediate ART for infected children <2 years of age irrespective of disease severity, and ART at much higher CD4 thresholds than before in older children.[2] This means that more children are starting therapy and increasingly those initiating treatment should have less advanced disease. Furthermore, although drug development, availability and accessibility for children lags behind that of adults,[3,4] there have been moves towards less toxic and more effective first-line ART.[2]

Timely ART initiation is important especially in infants and young children where pre-ART disease progression is rapid and mortality is high.[5,6] Even after ART initiation, early mortality remains very high in children with advanced disease, whereas starting ART with less advanced disease is associated with a good prognosis in terms of mortality, immunological, growth and neurodevelopmental outcomes.[7,8,9,10,11,12] There have been few articles published examining temporal trends in children initiating ART in sub-Saharan Africa.[13,14,15,16] During the early years of pediatric ART availability in South Africa between 2003 and 2007, ART initiation at 7 pediatric sites increased 3-fold and median baseline CD4% among children <5 years of age increased.[17] A later South African study (2005-2009) found that in later years children had less severe disease and there were increasing proportions both of very young (<18 months) and older (≥10 years) children initiating therapy.[13] Comparison of secular trends in a study of 565 children initiating ART at urban and rural clinics in Zambia showed trends towards decreasing age and increasing CD4% with later years, however the study was small and changes were not all significant.[14]

The International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration now includes individualized data on >35,000 children ever started on ART across 12 sites in southern Africa. This provides an opportunity to examine temporal trends in baseline characteristics and regimen use in a very large cohort across a range of settings in 4 countries (Malawi, South Africa, Zambia and Zimbabwe). This is important to determine the extent to which HIV care and treatment programmes have expanded and timely

ART initiation has improved in recent years, especially in relation to WHO and country guideline changes, as well as for program planning. In addition to examining characteristics across the cohort as a whole, we particularly aimed to focus on changes in infants starting therapy as the Children with HIV Early Antiretroviral Therapy (CHER) trial has shown that ART initiation in infants before disease progression substantially reduces mortality and morbidity.[2,12,18,19]

Methods

The IeDEA-SA collaboration has been described previously and currently includes 12 HIV care and treatment programs for children in 4 southern African countries (www.iedea-sa.org).[9,20] Data are collected prospectively at each site at ART initiation (baseline) and follow-up visits, using standardized definitions. Anonymized data are transferred to data centers at the Universities of Cape Town, South Africa, or Bern, Switzerland, in a standardized format and merged at regular intervals. All sites have institutional ethics approval for their local research ethics committee to contribute data to IeDEA-SA analyses. The IeDEA-SA Collaboration has been approved by the human research ethics committees of the Universities of Cape Town and Bern. We included all ART-naïve children (except for exposure to antiretrovirals to prevent mother to child transmission [PMTCT]) starting therapy at age <16 years between 1 January 2005 and 31 December 2010. Children starting before 2005 were excluded to limit the analysis to children likely to have presented after ART roll-out began. Children starting after 2010 were excluded as most cohorts transferred data during 2011 and so full data for that year is not available. The Hlabisa (South Africa) and Newlands (Zimbabwe) cohorts transferred data during 2010, and so did not contribute a full year of data for 2010. Children with a documented HIV-RNA measurement <400 copies/ml at baseline were excluded as they were unlikely to be ART-naïve.

Laboratory and anthropometric disease severity characteristics at ART start were the characteristics measured at the date closest to ART initiation within a window of -6 months to +7 days for CD4%/count, HIV-RNA and hemoglobin and a window of -1 month to +2 weeks for weight, height and body mass index (BMI). Weight-for-age, height-for-age and BMI-for-age z-scores (WAZ, HAZ, BAZ) were calculated using WHO 2006

standards.[21] BAZ was used rather than weight-for-height z-scores as these can be calculated for all ages, whereas weight-for-height standards are only available for children <5 years of age. Severe immune suppression was defined using the worst of CD4% and count, or whichever measure was available, using age-specific thresholds according to WHO guidelines.[22] Severe anemia was defined according to both hemoglobin and age using Division of AIDS criteria for grading of adverse events.[23]

We examined changes over the duration of the programme in continuous variables (using medians and interquartile ranges [IQR]) and in categorical variables (using proportions) for all children, and separately for those <1 year old at ART start. Changes in median values were assessed using the Cuzick's test for trend over the ordered groups of programme year. Changes in the proportion of patients with a particular disease severity characteristic (expressed as a binary variable e.g. WHO Stage III/IV vs I/II) over the duration of the programme were tested using logistic regression with the disease severity characteristic as the dependent variable and examining the linear trend over programme years as the independent variable. All analyses were done using STATA 12.0 (College Station, Texas, USA).

Results

Characteristics of all children starting therapy

Between 2005 and 2010, 30,300 ART-naïve children initiated ART at 12 IeDEA-SA treatment programs in 4 countries and were included in the analysis. There was considerable heterogeneity in program characteristics and the number (median 1,178; range across sites: 402-12,378), and characteristics of children initiating treatment at each program (Table 1; Figure 1; Supplementary Table S1). Programs ranged from single hospital facilities providing pediatric tertiary care to a number of clinics and hospitals providing all levels of care for adults and children across a health district or province. Median (IQR) age at ART initiation was 58 (20-109) months; range across sites 8-113. As expected with such heterogeneity in age, there was variability in CD4 count with median (IQR) of 381 (180-734) cells/mm^3; range across sites: 193-647. CD4% was less variable with median (IQR) of 14.0% (8.9-20.0); range across sites: 12.0-17.0. Overall, 70% of children were severely immunosuppressed and 72% had WHO Stage III/IV disease with ranges across sites of 54-84% and 28-93%

respectively. Median (IQR) WAZ was -2.01 (-3.23 to -0.97) and 29% of children <10 years old had WAZ<-3 (range across sites 13-40%). Variables were frequently not available for all children. Overall the proportions of missing data for WHO Stage, CD4 %/count, haemoglobin and weight were 19%, 34%, 47% and 22%. The median (IQR) number of days between variable measurement and ART start date was -21 (-44 to -9) (CD4 count), -23 (-46 to -12) (CD4%), -20 (-45 to 0) (HIV-RNA) -16 (-34 to -6) (haemoglobin) and 0 (0 to 0) for WAZ.

Changes in guidelines and temporal trends in child characteristics

Most programs followed national guidelines for ART initiation and first-line regimen choice which were based on WHO guidelines (Table 2).[24,25,26,27,28,29] There were sometimes lags or minor discrepancies between WHO recommendations and national guidelines. For example, while the WHO 2010 guidelines recommend ART initiation for all children <24 months old irrespective of disease severity, this was implemented in Zambia in 2011 and, until recently, South Africa had only implemented ART irrespective of disease severity for infants <12 months.

The number of children starting therapy increased each year from 3,849 in 2005 to 6,368 in 2009 (Figure 2). There was a slight decline in 2010, however 2 programs transferred data before the year ended. The median age dropped from a peak of 63 months in 2006 to 56 months in 2010 (p<0.001). Both the proportion of children <1 year and ≥10 years increased over time from 12 to 19% (p<0.001) and 18 to 22% (p<0.001) respectively. Children had less severe disease at ART initiation in later years for almost all markers – baseline CD4%/count increased and there were significant declines in the proportions with severe immunosuppression (81 to 63%; p<0.001), WHO Stage III/IV disease (75 to 62%; p<0.001) and severe anemia (12 to 7%; p<0.001) (Figure 2; Supplementary Table S3). Nutritional status improved slightly e.g. the proportion with WAZ <-3 decreased from 31 to 28% (p<0.001) and other nutritional indices showed similar trends. Completeness of data for most variables increased over time e.g. the proportion with missing data on weight and hemoglobin dropped from 30 to 18% and 60 to 41%. Notable exceptions were CD4%/count where the proportion of missing data was constant and HIV-RNA where it increased from 43% to 61%. Median HIV-RNA and proportion with >5 $\log_{10}$ showed a curious pattern of first decreasing and then increasing in 2010, however there was still a significant

trend to lower values in the later years. The increased values in 2010 may be due to both the younger age of infants starting ART and increasing coverage and effectiveness of PMTCT, with high HIV-RNA values in young infants infected despite PMTCT exposure.[30]

Temporal trends in characteristics of children <1 year of age

The number of children <1 year old at ART initiation more than doubled from 475 in 2005 to a peak of 1114 in 2009, with a slight drop in 2010. Median age at ART start in children <1 year dropped from 6.9 to 5.6 months. Children <1 year at ART start in later years had less severe disease. Median CD4%/count increased ($p<0.001$) and the proportion with severe immunodeficiency dropped from 98 to 82% and with WHO Stage III/IV disease from 81 to 63%. In 2005 nearly 60% of infants were severely underweight at ART start and this declined to 35% in 2010, with similar improvements in HAZ and BAZ.

First-line regimen

Almost all first-line regimens were an option selected from nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)1 (stavudine [d4T] / zidovudine [AZT] / abacavir [ABC] / tenofovir [TDF]) + NRTI2 (lamivudine [3TC] / emtricitabine [FTC]) + protease inhibitor (PI) / non-nucleoside reverse transcriptase inhibitor (NNRTI). First-line regimen differed for sites from within and outside South Africa and for children younger and older than 3 years. This is in keeping with national guidelines and drug prescribing information – dosing for efavirenz (EFV) is not established for children <3years/10kg; outside South Africa nevirapine (NVP) was recommended as the "third drug" for all children, while South African guidelines recommended PIs for children <3 years/10kg, and EFV in older children. Across all age groups, 3TC predominated as NRTI2.

NRTI1: Outside South Africa d4T use predominated and increased over time from 61% to 81% ($p<0.001$) and 66% to 71% ($p<0.001$) in children below and above 3 years of age, with corresponding declines in AZT use. There were also small increases over time in ABC use for all children and TDF for children >3 years. Within South Africa d4T use increased slightly in children <3years from 2005 to 2009 (83 to 89%) with corresponding declines in AZT, but was constant at 96-97% in older children. In both age groups a change was seen in 2010 with proportion starting d4T dropping to 41% and 60% in children younger and older than 3 years, with ABC replacing d4T as the NRTI1 of choice. There was negligible use of TDF.

NNRTI/PI: Outside South Africa NVP use predominated in both age groups: 97 and 87% of children younger and older than 3 years. Almost all of the remainder of children initiated EFV, use of which increased over time in older children from 8 to 16% ($p<0.001$). There was negligible use of PIs. Inside South Africa in children <3 years, NVP use declined from 9% in 2005 to <1% in 2010 ($p<0.001$) with corresponding increases in lopinavir-ritonavir (LPV/r) use. In 2005 and 2006, 11% of children <3 years initiated therapy with ritonavir alone as the third drug, but this was almost completely eliminated from 2007 onwards when LPV/r dosing recommendations for children <6 months of age were introduced and double dose LPV/r or ritonavir-boosted LPV/r were used when co-treating for tuberculosis. EFV predominated in children >3 years (93% of children) with no temporal changes.

Discussion:

This analysis of >30,000 children who started ART across Southern Africa between 2005 and 2010 demonstrates that not only is the number of children starting therapy increasing, but also that in recent years children are younger and less severely ill at ART start. Nevertheless, even in 2010 many children were still initiating therapy with advanced disease – 62% with WHO Stage III/IV disease, 29% with WAZ<-3 and 63% were severely immunosuppressed.

Similar temporal trends in disease severity characteristics were noted in a South African study of 3,000 children initiating therapy at 30 health facilities between 2005 to 2009 [13], as well as in Zambia[14]. Initiating therapy earlier in the course of disease is important as children with less severe disease experience better outcomes on ART and, in particular, the high early mortality seen in children starting therapy in resource-limited settings may be attenuated.[7,31,32,33,34,35,36] Early ART also improves neurodevelopmental outcomes in infants.[12] Indeed both the South African and Zambian studies showed temporal improvements in mortality.[13,14] As has been found in adult studies, however, in Zambia there was also increasing loss to follow-up over time which may include unascertained mortality.[14,37,38] Encouragingly in the South African study loss to follow-up did not increase over time.[13]

It appears there is a mixed pattern of temporal trends in age with increasing proportions of infants as well as older children and adolescents initiating therapy.[13] Despite temporal increases, the proportion of infants initiating therapy in our study was still low reaching 19% in 2010. Nevertheless this is substantially higher than in previously published studies and may be due to the inclusion of data from 2010 after most countries had adopted universal ART for children <1 year, as well as inclusion of 2 sites providing exclusive tertiary care in South Africa where >50% of children were infants. The proportion of children starting therapy at <1 year of age is complex as it is a composite result of the ability of health care services to promptly diagnose and initiate infants on therapy, the coverage and effectiveness of PMTCT programs in reducing numbers of newly infected infants, as well as the backlog of older children not yet initiated on therapy. The latter may be substantial and is an important consideration in designing pediatric HIV care and ART programs as the needs and disease spectrum in these children are different from infants and toddlers.[39,40,41] In our study 1,151 children ≥10 years of age (22% of all children) initiated therapy, however these were not all confirmed to be infected perinatally, rather than through sexual transmission. Other studies have found considerable numbers of perinatally infected children being diagnosed with HIV in late childhood or adolescence.[39,42,43]

Despite temporal improvements across all ages in disease severity at ART start, the proportion of children initiating therapy with severe disease even at the end of the analysis period is a concern. Even in 2010, the median CD4%, WAZ and $\log_{10}$ HIV-RNA in our study indicated markedly more severe disease than those from a review of studies from developed countries.[8] This is particularly the case for infants where early ART initiation before disease progression substantially reduces mortality and morbidity.[18] In our study in 2010, >60% of infants started therapy with WHO Stage III/IV disease and >80% with severe immune suppression. The median age of infants starting ART in 2010 was 5.6 months which is well above the median age of <2 months in the immediate arm of the CHER Study. There are a number of barriers to early ART initiation including lack of access to HIV-DNA PCR testing for diagnosis,[24,44,45,46] poor integration of antenatal, PMTCT, maternal and child health (MCH) and HIV services with poor infant HIV testing even among those whose mothers enrolled in PMTCT care,[47] lack of expertise, experience and confidence with initiating and maintaining infants on ART and poor availability of drugs in suitable formulations for infants.[4,48] Strategies

to improve ART access for infants such as integration of PMTCT, MCH and HIV services and provider initiated testing at vaccination and other health visits[49,50,51,52] need to be developed and expanded. In Zambia, the median age of children enrolling in HIV care declined in settings where there was close collaboration between the MCH service and the ART clinic.[14] Notwithstanding these measures, disease progression in infants, especially those infected *in utero*, is extremely rapid – 25% of 560 HIV-infected infants identified at <12 weeks old as potential participants in the CHER study were ineligible as they already had CD4%<25, symptomatic disease or had died before screening/enrolment.[18] Currently infant diagnostic testing is recommended at 6 weeks of age, with ART initiation in infected infants at 10-14 weeks of age. However, in a study to determine optimal timing of infant diagnostic testing, it was found that 45% of *in utero*-infected and 22% of *intrapartum*-infected infants had died or were lost to follow-up by 14 weeks of age.[53] The role of earlier PCR testing in infants needs to be explored.

First-line regimen use closely followed national guidelines. PI use was almost completely absent outside of South Africa, but this is likely to change following the results of the P1060 trial that demonstrated better survival and virological outcomes in children <3 years old initiating PI based compared to NNRTI-based therapy, irrespective of prior PMTCT exposure.[54] Similarly while TDF use was very limited, this is likely to increase with the WHO/UNAIDS Treatment 2.0 strategy that aims to harmonize guidelines across ages and may advise TDF use in children >5 years of age. The feasibility, cost and long term outcomes of these changes will need to be examined.

To our knowledge this is the largest study of temporal trends in child characteristics at the start of ART in sub-Saharan Africa and the only study including a range of settings in more than one country to date. The number of children in our study is nearly 10% of the 337,200 children estimated to be receiving ART in eastern and southern Africa by the end of 2010.[1] Inclusion of data from 3 different periods of WHO guidelines enabled us to comment on how patient characteristics at ART start have changed as a result of WHO and national guideline changes. Representativeness of all children initiating ART in the region may however be limited as cohorts contributing to IeDEA-SA must have electronic patient databases and so are likely to be better resourced than all programs in the region. Nevertheless, the use of routine program data from busy clinics in

this analysis, rather than dedicated research databases, enhances representativeness. There was substantial missing data on a number of variables, but this is true of routine monitoring data from many settings, and it is encouraging that the proportion of missing data for most variables decreased in later years.[13,34] Data on key variables of interest such as PMTCT exposure and tuberculosis infection at ART start were too sparse to include in the analysis.

In conclusion, over time increasing numbers of children are initiating ART at younger ages and with less severe disease in these programs. However the proportion of infants remains low and proportion of children across all ages initiating ART with severe disease remains high. It is important to continue to develop strategies for earlier diagnosis and treatment of infants as well as to examine long term outcomes in the era of expanding coverage of pediatric HIV and more effective PMTCT.

Acknowledgements

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Table 1: Characteristics of cohorts

Cohort name and location	Main level of care provided	Multiple facilities	Type of clinic and payment	Target population	Number of children ever started on ART since program start	Number of children included in the analysis (started ART between 1 Jan 2005 and 31 Dec 2010)
Zambian MOH-CIDRZ, Lusaka, Zambia	Primary	Yes	Public, Free ART	Adults and children, combined clinics	14,500	12,378
Free State Province, South Africa	All levels	Yes	Public and research, Free ART	Adults and children, combined clinics	4,629	4,579
Gugulethu Community Health Centre, Cape Town, South Africa	Primary	No	Public and research, Free ART	Adults and children, separate clinics	483	402
Hlabisa HIV Care and Treatment Programme, Kwazulu-Natal, South Africa	Primary	Yes	Public, Free ART	Adults and children, combined clinics	1,141	1,134
Harriet Shezi, Chris Hani Baragwanath Hospital, Soweto, South Africa	All levels	No	Public and research, Free ART	Children only	4,629	3,996
Khayelitsha Community Health Centre, Cape Town, South Africa	Primary	Yes	Public, Free ART	Adults and children, separate clinics	1,191	919
Lighthouse Clinic, Kamuzu Central Hospital, Lilongwe, Malawi	All levels	No	Public, Free ART	Adults and children, combined clinics	1,416	1,221
McCord Hospital, Durban, South Africa	Secondary	No	Private not-for-profit; Small co-payment	Adults and children, separate clinics	804	735
Newlands Clinic, Harare, Zimbabwe	Secondary	No	Public, Free ART	Adults and children, separate clinics	874	829
Red Cross Children's Hospital, Cape Town, South Africa	Tertiary	No	Public and research; Free ART	Children only	1,873	1,360
Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa	All levels	No	Public, Free ART	Children and pregnant women	2,198	1,854
Tygerberg Hospital, Cape Town, South Africa	Tertiary	No	Public and research, Free ART	Adults and children, separate clinics	1,307	893
TOTAL					**35,045**	**30,300**

Table 2: Country guidelines for ART for children from 2004 – 2011.

<table>
<tr><td>GUIDELINE</td><td colspan="4">WHO</td><td colspan="3">Malawi</td><td colspan="2">South Africa</td><td colspan="4">Zambia</td><td colspan="3">Zimbabwe</td></tr>
<tr><td>YEAR</td><td>2004 - 2005</td><td>2006 - 2007</td><td>2008 -2009</td><td>2010 onwards</td><td>2006 - 2007</td><td>2008 - 2010</td><td>2011 onwards</td><td>2004-2009</td><td>2010 onwards</td><td>2004-2005</td><td>2006-2008</td><td>2009 and 2010</td><td>2011 onwards</td><td>2005-2006</td><td>2007-2009</td><td>2010 onwards</td></tr>
<tr><td rowspan="6">ART initiation criteria</td><td colspan="4" rowspan="2">WHO Stage III or IV disease</td><td><18 mos, presumptive HIV diagnosis: WHO Stage IV</td><td colspan="2" rowspan="2">WHO Stage III or IV</td><td colspan="2" rowspan="2">WHO Stage III/IV disease</td><td colspan="4" rowspan="2">WHO Stage III/IV disease</td><td colspan="3" rowspan="2">WHO Stage III/IV disease</td></tr>
<tr><td>>18 mos, definite HIV diagnosis: WHO Stage III/IV disease</td></tr>
<tr><td><18 mos: CD4% <20</td><td>≤11 mos: CD4 <1500 or 25%</td><td>≤11 mos: all</td><td rowspan="2"><24 mos: all</td><td rowspan="2"><18 mos (presumptive diagnosis): ≥2 of oral candidiasis, severe pneumonia or severe sepsis <12 mos: CD4% <25</td><td rowspan="2">≤11 mos: all</td><td rowspan="4">As for WHO 2010</td><td>Recurrent (>2/yr) or prolonged (>4 wks) hospitalizations for HIV-related illness</td><td>≤11 mos: all</td><td rowspan="4">as for who 2004-2005</td><td rowspan="4">as for WHO 2006-2007</td><td rowspan="4">as for WHO 2008-2009</td><td rowspan="4">as for WHO 2010</td><td><18 mos: CD4% <25</td><td rowspan="4">as for WHO 2006-2007</td><td>≤11 mos: all</td></tr>
<tr><td rowspan="3">≥18 mos: CD4% <15</td><td colspan="2">12 to 35 mos: CD4 <750 or 20%</td><td><18 mos: CD4% <20</td><td rowspan="3">12 - 59 mos: CD4 <750 or 25%</td><td rowspan="3">18 mos to 5 years: CD4% <15</td><td rowspan="3">12-59 mos: CD4% <25</td></tr>
<tr><td colspan="2" rowspan="2">36 to 59 mos: CD4 <350 or 15%</td><td rowspan="2">24 - 59 mos: CD4 ≤750 or ≤25%</td><td>12 - 18 mos: CD4 <20%</td><td rowspan="2">≥18 mos: CD4% <15</td></tr>
<tr><td>18 to 35 mos: CD4 <750 or 20%</td></tr>
<tr><td colspan="2">≥5 years: CD4 <200 or 15%</td><td>≥5 years: CD4 ≤350</td><td colspan="2">36 to 59 mos: CD4 <350 or 15%</td><td>≥5 years: CD4 <250 or 15%</td><td>≥5 years: CD4 <350</td><td>≥5 years: CD4 <200</td><td>≥5 years: CD4 <350</td></tr>
<tr><td>GUIDELINE</td><td colspan="4">WHO</td><td colspan="3">Malawi</td><td colspan="2">South Africa</td><td colspan="4">Zambia</td><td colspan="3">Zimbabwe</td></tr>
<tr><td>YEAR</td><td>2004 - 2005</td><td>2006 - 2007</td><td>2008 -2009</td><td>2010 onwards</td><td>2006 - 2007</td><td>2008 - 2010</td><td>2011 onwards</td><td>2004-2009</td><td>2010 onwards</td><td>2004-2005</td><td>2006-2008</td><td>2009 and 2010</td><td>2011 onwards</td><td>2005-2006</td><td>2007-2009</td><td>2010 onwards</td></tr>
<tr><td rowspan="4">First line regimen</td><td>NRTI 1</td><td>AZT/d4T</td><td colspan="3">AZT/d4T/ABC</td><td colspan="2">d4T</td><td>AZT</td><td>d4T</td><td>ABC</td><td colspan="4">AZT/d4T</td><td>AZT</td><td>AZT/d4T</td><td>AZT</td></tr>
<tr><td>NRTI 2</td><td colspan="4">3TC</td><td colspan="3">3TC</td><td colspan="2">3TC</td><td colspan="4">3TC</td><td colspan="3">3TC</td></tr>
<tr><td rowspan="2">Third ARV</td><td colspan="3" rowspan="2">NVP/EFV (EFV only if >3 yrs and >10 kg)</td><td><24 mos; no prior NVP exposure: NVP</td><td colspan="3" rowspan="2">NVP</td><td>6mos - 3 yrs: LPV/r (ritonvair alone for children < 6 mos or co-treated for TB)</td><td><3 yrs: LPV/r</td><td rowspan="2">NVP/EFV</td><td>LPV/r (prior NVP exposure)</td><td><24 mos; no prior NVP exposure: NVP</td><td rowspan="2">NVP</td><td>LPV/r (prior NVP exposure)</td></tr>
<tr><td><24 mos; prior NVP exposure: LPV/r</td><td colspan="2">>3 yrs and >10kg: EFV</td><td rowspan="2">NVP/EFV (no prior NVP exposure)</td><td><24 mos; prior NVP exposure: LPV/r</td><td rowspan="2">NVP/EFV (no prior NVP exposure)</td></tr>
<tr><td>≥24 mos: NVP/EFV</td><td>≥24 mos: NVP/EFV</td></tr>
</table>

Figure 1: Short title: Characteristics of children at ART start in the different cohorts

Figure 1: Legend: Characteristics of children at ART start in the different cohorts (median [IQR] age, weight-for-age z-score [WAZ], CD4 count and percent).

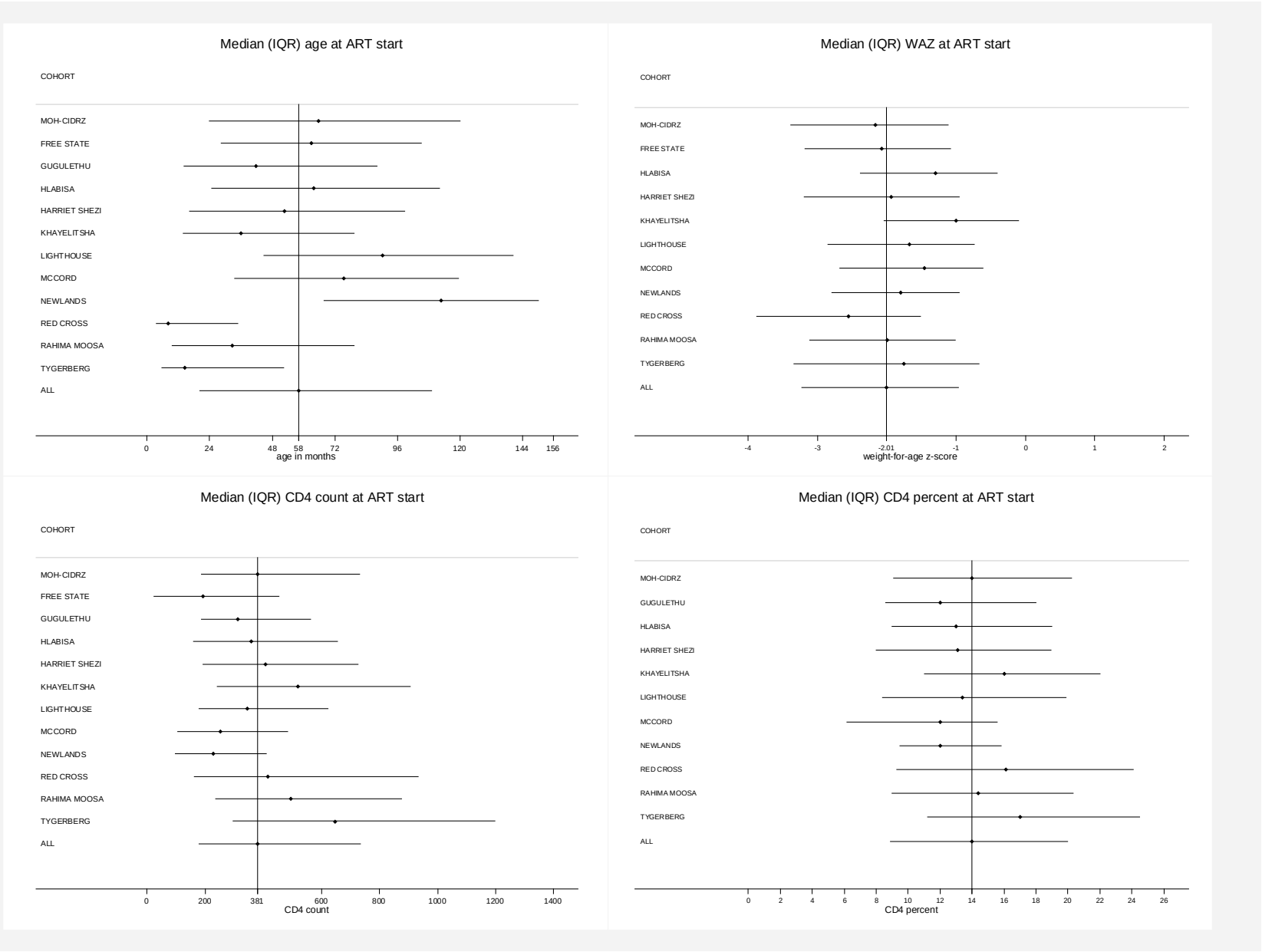


Figure 2: Short title: Characteristics of children at ART start by programme year

Figure 2: Legend: Characteristics of children at ART start by programme year summarized as medians for continuous variables and proportions for categorical variables. p <0.001 for changes over programme year for all variables (Cuzick's test for trend for continuous variables and logistic regression for categorical variables). (Note: Only children <10 years of age included in weight-for-age z-score graphs and only South African sites included for graphs of HIV-RNA.)

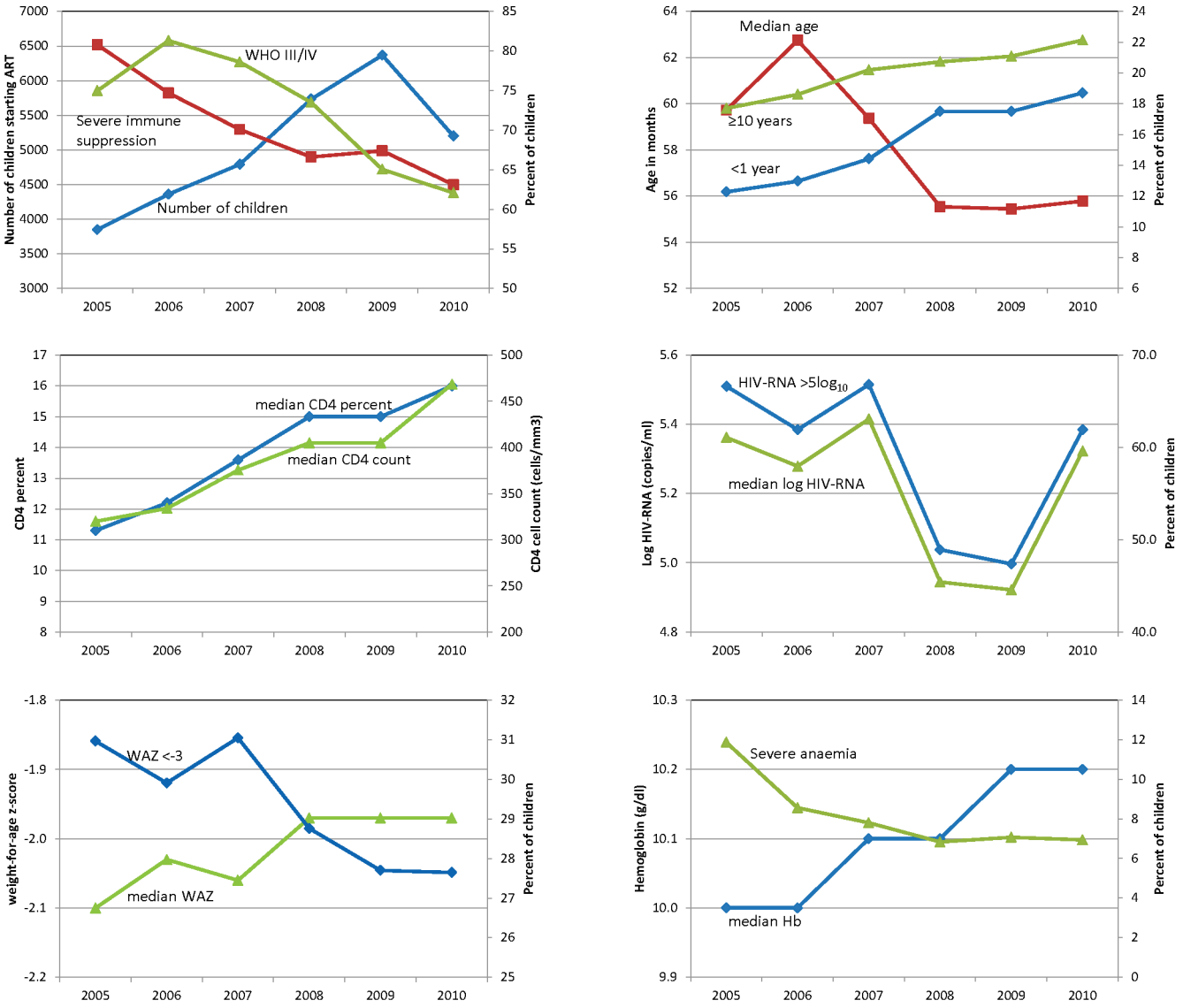
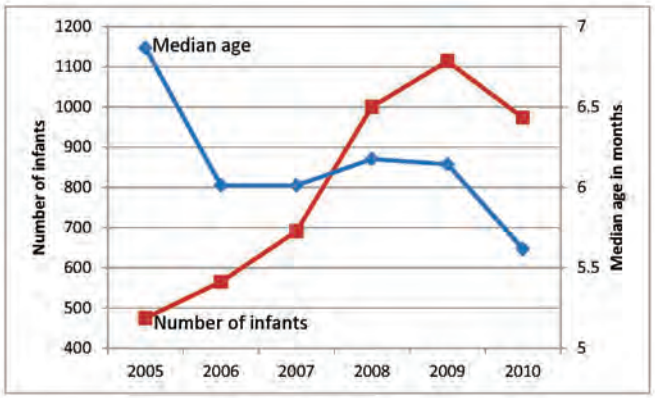
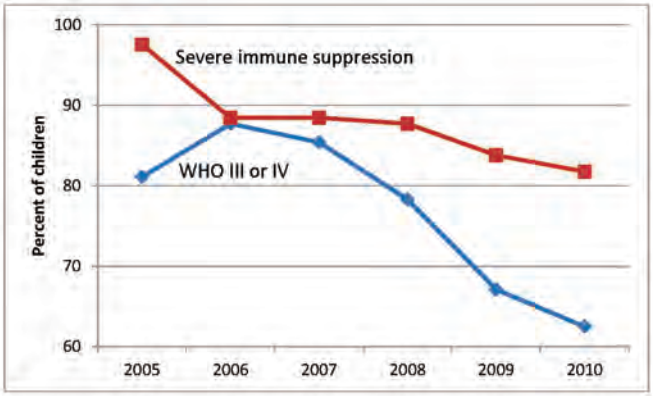
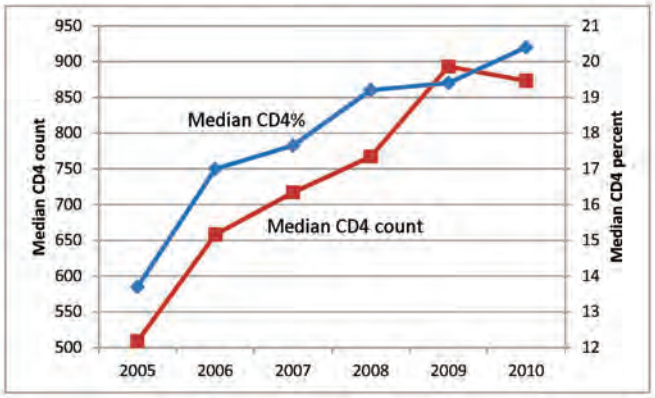


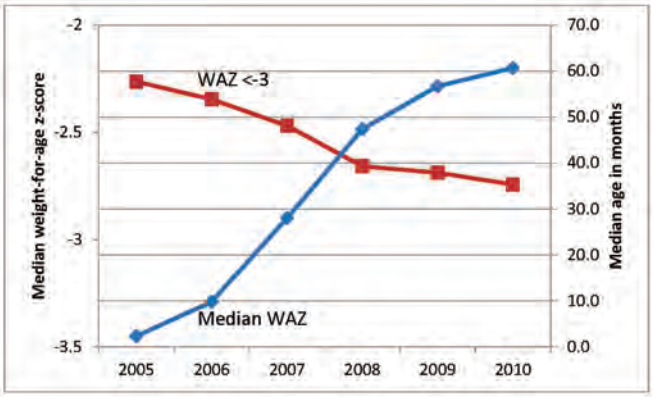
Figure 3: Short title: Characteristics of children <1 year of age at ART start by programme year.

Figure 3: Legend: Characteristics of children <1 year of age at ART start by programme year summarized as medians for continuous variables and proportions for categorical variables. p<0.001 for changes over programme year for all variables (Cuzick's test for trend for continuous variables and logistic regression for categorical variables).









Supplementary Tables

Appendix Table S1: Characteristics of children at ART initiation in each cohort for (a) continuous variables and (b) categorical variables

a)

	Age in months			CD4 percent			CD4 absolute count (cells/mm3)			Haemoglobin (g/dl)			Log_{10} HIV-RNA[$]			Weight-for-age z-score[*]			Height-for-age z-score			BMI-for-age z-score		
Cohort	**N**	**median**	**IQR**	**N**	**median**	**IQR**	**N**	**median**	**IQR**	**N**	**median**	**IQR**	**N**	**median**	**IQR**	**N**	**median**	**IQR**	**N**	**median**	**IQR**	**N**	**median**	**IQR**
CIDRZ	12378	66	24 to 120	7623	14.0	9.1 to 20.2	9753	381	187 to 733	9569	10.0	8.8 to 11.2				8729	-2.17	-3.39 to -1.11	8970	-2.59	-3.75 to -1.48	8978	-0.80	-2.06 to 0.37
Free State	4579	63	28 to 105				360	193	23 to 455	292	11.0	9.0 to 12.0	273	5.00	4.53 to 5.6	1721	-2.08	-3.18 to -1.08						
Gugulethu	402	42	14 to 88	183	12.0	8.6 to 18.0	199	312	187 to 564	183	10.5	9.7 to 11.1	194	4.93	4.55 to 5.45									
Hlabisa	1134	64	25 to 112	951	13.0	9.0 to 19.0	967	359	159 to 655	885	10.1	9.2 to 11.1	540	4.45	3.86 to 5.20	828	-1.29	-2.39 to -0.41	96	-2.00	-2.95 to -0.82	98	-0.66	-2.29 to 0.27
Harriet Shezi	3996	53	16 to 99	3000	13.1	8.0 to 19.0	2975	407	192 to 726	1385	10.5	9.5 to 11.6	2788	5.15	4.49 to 5.80	3092	-1.94	-3.20 to -0.96	3555	-2.42	-3.41 to -1.50	3552	-0.55	-1.75 to 0.36
Khayelitsha	919	36	14 to 79	423	16.0	11.0 to 22.0	543	520	241 to 907	20	10.0	9.0 to 11.0	344	5.19	4.45 to 5.85	764	-1.00	-2.04 to -0.10	104	-1.98	-3.05 to -0.84	103	-0.18	-1.38 to 1.21
Ligthouse	1221	90	45 to 140	614	13.4	8.4 to 19.9	688	346	178 to 623	211	10.4	9.1 to 11.2				649	-1.68	-2.85 to -0.74	761	-2.42	-3.42 to -1.50	762	-0.42	-1.40 to 0.37
McCord	735	75	34 to 120	616	12.0	6.1 to 15.5	626	254	106 to 485	483	10.2	9.2 to 11.1	36	5.51	4.80 to 6.26	192	-1.46	-2.68 to -0.61	172	-2.07	-3.00 to -1.29	172	-0.17	-1.37 to 0.70
Newlands	829	113	68 to 150	26	12.0	9.5 to 15.8	741	227	96 to 411	743	10.8	9.8 to 11.9				423	-1.80	-2.79 to -0.95	740	-2.48	-3.36 to -1.59	740	-0.75	-1.72 to 0.11
Red Cross	1360	8	3 to 35	847	16.1	9.3 to 24.1	834	416	162 to 932	843	9.8	8.6 to 11.0	749	5.84	5.15 to 6.36	941	-2.56	-3.88 to -1.51	740	-2.45	-3.60 to -1.40	748	-1.70	-3.3 to -0.63
Rahima Moosa	1854	33	10 to 79	1247	14.4	9.0 to 20.3	1241	495	237 to 877	632	10.5	9.4 to 11.5	1123	5.36	4.69 to 6.00	1192	-1.99	-3.11 to -1.01	1304	-2.13	-3.16 to -1.15	1308	-0.90	-2.22 to 0.16
Tygerberg	893	14	6 to 53	746	17.0	11.2 to 24.5	782	647	295 to 1197	750	10.0	8.8 to 11.0	620	5.58	4.92 to 6.20	534	-1.75	-3.34 to -0.67	537	-2.16	-3.13 to -1.11	536	-0.60	-2.20 to 0.44
All	30300	58	20 to 109	16276	14.0	8.9 to 20.0	19709	381	180 to 734	15996	10.1	9.0 to 11.3	6848	5.23	4.53 to 5.89	19065	-2.01	-3.23 to -0.97	16979	-2.46	-3.56 to -1.45	16997	-0.75	-2.03 to 0.32

[*]Children < 10 years of age

[$]South African sites only

	age <1 year		age ≥10		WHO Stage III or IV				Severe immune				Severe anaemia				HIV-RNA >5log_{10}[*]				WAZ <-3[#]				HAZ <-3				BAZ <-3			
Cohort					Yes		NR		Yes		NR		Yes		NR		Yes		NR		Yes		NR		Yes		NR		Yes		NR	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
CIDRZ	1,230	10	3,095	25	7,989	67	459	4	6,511	66	2579	21	883	9	2809	23					2836	33	623	7	3587	40	3408	28	1,233	14	3400	27
Free State	499	11	804	18	551	28	2592	57	234	65	4219	92	20	7	4287	94	137	50	4,306	94	481	28	2063	55			4579	100			4579	100
Gugulethu	93	23	48	12	285	72	8	2	146	74	203	51	8	4	219	54	91	47	208	52			354	100			402	100			402	100
Hlabisa	105	9	237	21	830	81	111	10	718	74	159	14	42	5	249	22	166	31	594	52	117	14	72	8	22	23	1038	92	16	16	1036	91
Harriet Shezi	797	20	600	15	3307	95	519	13	2282	75	973	24	61	4	2611	65	1,552	56	1,208	30	849	28	322	9	1214	34	441	11	427	12	444	11
Khayelitsha	208	23	92	10	679	75	11	1	398	67	322	35	1	5	899	98	191	56	575	63	97	13	67	8	27	26	815	89	7	7	816	89
Lighthouse	44	4	427	35	1028	93	117	10	460	67	532	44	10	5	1,010	83					136	21	154	19	264	35	460	38	47	6	459	38
McCord	76	10	183	25			735	100	524	84	108	15	21	4	252	35	25	69	699	95	40	21	364	66	43	25	563	76	14	8	563	77
Newlands	19	2	364	44	89	72	706	85	397	54	88	11	19	3	86	10					92	22	49	11	260	35	89	11	80	11	89	11
Red Cross	789	58	65	5	1149	86	22	2	691	81	509	37	85	10	517	38	586	78	611	45	373	40	357	28	274	37	620	46	222	30	612	45
Rahima Moosa	541	29	172	9	1002	68	373	20	958	77	605	33	36	6	1222	66	727	65	731	39	332	28	497	29	366	28	550	30	210	16	546	29
Tygerberg	417	47	54	6	639	88	167	19	574	73	107	12	58	8	143	16	447	72	273	31	162	30	307	37	149	28	356	40	73	14	357	40
Total	**4,818**	**16**	**6141**	**20**	**17,776**	**72**	**5,915**	**19**	**13893**	**70**	**10404**	**34**	**1244**	**8**	**14304**	**47**	**3,922**	**59**	**9,205**	**58**	**5515**	**29**	**5229**	**22**	**6,259**	**36**	**13321**	**44**	**2329**	**14**	**13303**	**44**

NR = Not recorded

[*]South African sites only

[#]Children < 10 years of age

b)

Appendix table S2 (a): Median (IQR) values of characteristics at antiretroviral therapy initiation for children by programme year from 2005 to 2010.

Programme year	2005	2006	2007	2008	2009	2010	p-value[#]
age							
n	3849	4360	4791	5732	6368	5200	
median	60	63	59	56	55	56	<0.001
IQR	24 to 103	24 to 107	22 to 108	18 to 110	18 to 111	18 to 113	
CD4 percent							
n	2270	2355	2431	2883	3404	2933	
median	11.3	12.2	13.6	15.0	15.0	16.0	<0.001
IQR	7 to 15.7	7.5 to 17.8	8.9 to 19.3	9.8 to 21.7	9.8 to 21.2	10.4 to 22.5	
CD4 count							
n	2681	2884	3082	3559	4113	3390	
median	320	334	376	405	405	469	<0.001
IQR	140 to 575	150 to 624	174 to 710	198 to 765	196 to 789	217 to 885	
Log_{10} HIV-RNA[*]							
n	1264	1195	991	1178	1102	937	
median	5.36	5.28	5.41	4.94	4.92	5.32	<0.001
IQR	4.81 to 5.94	4.69 to 5.89	4.74 to 6.15	4.26 to 5.74	4.20 to 5.72	4.61 to 6.06	
WAZ							
n	2225	2574	2982	3679	4267	3338	
median	-2.10	-2.03	-2.06	-1.97	-1.97	-1.97	<0.001
IQR	-3.35 to -1.05	-3.26 to -1.03	-3.35 to -0.98	-3.22 to -0.97	-3.17 to -0.92	-3.15 to -0.94	
HAZ							
n	1812	2207	2687	3463	3695	3115	
median	-2.69	-2.52	-2.46	-2.41	-2.46	-2.32	<0.001
IQR	-3.7 to -1.67	-3.57 to -1.51	-3.59 to -1.44	-3.52 to -1.39	-3.64 to -1.43	-3.37 to -1.31	
BAZ							
n	1815	2208	2704	3450	3696	3124	
median	-0.74	-0.81	-0.82	-0.76	-0.71	-0.69	0.01
IQR	-2.11 to 0.38	-2.08 to 0.28	-2.11 to 0.28	-1.97 to 0.26	-1.94 to 0.38	-2.01 to 0.38	
Haemoglobin							
n	1536	1957	2444	3101	3873	3085	
median	10.0	10.0	10.1	10.1	10.2	10.2	<0.001
IQR	8.6 to 11.1	8.9 to 11.3	8.9 to 11.2	9 to 11.2	9.1 to 11.3	9.1 to 11.3	

[*]South African sites only

[#]Cuzick's test for trend over ordered groups

Appendix table S2(b): Proportion of children in each age group and with particular disease severity characteristics or missing data by programme year.

Programme Year		2005	2006	2007	2008	2009	2010	p-value[#]
Age category								
<1 year	n	475	565	691	1,000	1,114	973	<0.001
	% of all children	12.3	13.0	14.4	17.5	17.5	18.7	
1 year	n	475	540	621	801	867	725	
	% of all children	12.3	12.4	13.0	14.0	13.6	13.9	
2 - 4 years	n	981	1,013	1,094	1,182	1,331	990	
	% of all children	25.5	23.2	22.8	20.6	20.9	19.0	
5-9 yrs	n	1,238	1,431	1,417	1,561	1,713	1,361	
	% of all children	32.2	32.8	29.6	27.2	26.9	26.2	
≥10 years	n	680	811	968	1,188	1,343	1,151	<0.001
	% of all children	17.7	18.6	20.2	20.7	21.1	22.1	
WHO Stage III/IV	n	2,247	2,715	3,003	3,430	3,455	2,698	<0.001
	% of available data	75.0	81.3	78.6	73.5	65.0	62.1	
NR	n	852	1,021	971	1,066	1,056	854	
	% of all children	22.1	23.4	20.3	18.6	16.6	16.4	
WAZ < -3	n	689	770	926	1,058	1,182	923	<0.001
	% of available data	31.0	29.9	31.1	28.8	27.7	27.7	
NR	n	970	1,001	869	887	786	741	
	% of all children	30.4	28.1	22.6	19.4	15.6	18.2	
HAZ < -3	n	744	809	973	1,242	1,395	1,043	<0.001
	% of available data	41.1	36.7	36.2	35.9	37.8	33.5	
NR	n	2,037	2,153	2,104	2,269	2,673	2,085	
	% of all children	52.9	49.4	43.9	39.6	42.0	40.1	
BAZ < -3	n	278	308	383	453	501	406	0.025
	% of available data	15.3	14.0	14.2	13.1	13.6	13.0	
NR	n	2,034	2,152	2,087	2,282	2,672	2,076	
	% of all children	52.8	49.4	43.6	39.8	42.0	39.9	
Severe anaemia	n	183	168	192	210	274	217	<0.001
	% of available data	11.9	8.6	7.8	6.8	7.1	6.9	
NR	n	2,313	2,403	2,347	2,631	2,495	2,115	
	% of all children	60.1	55.1	49.0	45.9	39.2	40.7	
HIV-RNA >5 $\log_{10}$[*]	n	842	740	662	576	522	580	<0.001
	% of available data	66.6	61.9	66.8	48.9	47.4	61.9	
NR	n	946	1,307	1,525	1,871	2,085	1,471	
	% of all children	42.8	52.2	60.6	61.4	65.4	61.1	
Severe immune suppression	n	2,187	2,179	2,177	2,396	2,792	2,162	<0.001
	% of available data	80.8	74.7	70.1	66.6	67.4	63.1	
NR	n	1,142	1,443	1,685	2,135	2,225	1,774	
	% of all children	29.7	33.1	35.2	37.3	34.9	34.1	

NR = not reported

[*]South African sites only

[#]p-values derived from logistic regression of binary dependent variable with programme year as an independent variable

Appendix Table S3 (a): Median (IQR) values of characteristics at ART initiation for children <1 year of age at ART start by programme year from 2005 to 2010.

Programme Year		2005	2006	2007	2008	2009	2010	p-value[#]
Age in months	**n**	475	565	691	1000	1114	973	
	median	6.9	6.0	6.0	6.2	6.1	5.6	<0.001
	IQR	4.5 to 9.4	4 to 8.7	3.5 to 8.9	3.9 to 9	3.8 to 8.8	3.4 to 8.7	
CD4 percent	**n**	307	347	404	574	678	567	
	median	13.7	17.0	17.7	19.2	19.4	20.4	<0.001
	IQR	8.9 to 20	10.7 to 24.9	11.9 to 24	13 to 26.5	13.4 to 26.4	13.2 to 28	
CD4 count	**n**	317	363	422	615	722	610	
	median	509	658	717	767	893	873	<0.001
	IQR	197 to 1013	299 to 1202	347 to 1222	364 to 1274	388 to 1511	429 to 1477	
Log10 HIV-RNA*	**n**	250	287	275	368	363	280	
	median	6.00	6.01	6.30	5.83	5.82	6.06	0.06
	IQR	5.53 to 6.32	5.46 to 6.48	5.79 to 6.48	5.20 to 6.30	5.15 to 6.30	5.36 to 6.51	
WAZ	**n**	319	351	503	776	900	742	
	median	-3.45	-3.29	-2.90	-2.49	-2.28	-2.20	<0.001
	IQR	-4.61 to -2.21	-4.37 to -1.82	-4.17 to -1.52	-3.8 to -1.15	-3.79 to -0.93	-3.49 to -0.83	
HAZ	**n**	251	285	390	559	596	507	
	median	-3.03	-3.14	-2.68	-2.43	-2.19	-2.17	<0.001
	IQR	-4.23 to -1.58	-4.15 to -1.81	-4.06 to -1.14	-3.73 to -1.07	-3.82 to -0.98	-3.54 to -0.9	
BMI-age z	**n**	259	287	401	558	602	519	
	median	-2.74	-2.08	-1.83	-1.65	-1.43	-1.44	<0.001
	IQR	-4.01 to -1.07	-3.44 to -0.91	-3.26 to -0.35	-3.16 to -0.4	-3.23 to 0.04	-3.09 to 0.13	
Haemoglobin	**n**	155	223	333	541	670	561	
	median	9.9	9.8	9.5	9.6	9.8	9.8	0.08
	IQR	8.3 to 10.8	8.5 to 11	8.5 to 10.8	8.7 to 10.8	8.8 to 10.9	8.7 to 10.8	

*South African sites only

[#]Cuzick's test for trend

Appendix Table S3 (b): Proportion of children <1 year of age at ART start with particular disease severity characteristics or missing data by programme year from 2005 to 2010.

Programme year		2005	2006	2007	2008	2009	2010	p-value[#]
WHO Stage III or IV	**n**	308	400	492	662	656	519	
	% of available data	81.1	87.7	85.4	78.3	67.1	62.5	<0.001
NR	**n**	95	109	115	154	137	143	
	% of all children	20.0	19.3	16.6	15.4	12.3	14.7	
WAZ <-3	**n**	184	189	242	305	341	262	
	% of available data	57.7	53.9	48.1	39.3	37.9	35.3	<0.001
NR	**n**	156	214	188	224	214	231	
	% of all children	32.8	37.9	27.2	22.4	19.2	23.7	
HAZ <-3	**n**	127	149	163	221	228	171	
	% of available data	50.6	52.3	41.8	39.5	38.3	33.7	<0.001
NR	**n**	224	280	301	441	518	466	
	% of all children	47.2	49.6	43.6	44.1	46.5	47.9	
BAZ <-3	**n**	115	87	118	148	172	131	
	% of available data	44.4	30.3	29.4	26.5	28.6	25.2	<0.001
NR	**n**	216	278	290	442	512	454	
	% of all children	45.5	49.2	42.0	44.2	46.0	46.7	
Severe anaemia	**n**	22	23	34	35	54	46	
	% of available data	14.2	10.3	10.2	6.5	8.1	8.2	0.022
NR	**n**	320	342	358	459	444	412	
	% of all children	67.4	60.5	51.8	45.9	39.9	42.3	
Severe immune	**n**	318	329	383	556	620	515	
suppression	**% of available data**	97.6	88.4	88.5	87.7	83.8	81.8	<0.001
NR	**n**	149	193	258	366	374	343	
	% of all children	31.4	34.2	37.3	36.6	33.6	35.3	
HIV-RNA >5log10*	**n**	223	255	257	294	288	231	
	% of available data	89.2	88.9	93.5	79.9	79.3	82.5	<0.001
NR	**n**	167	215	252	367	363	338	
	% of all children	40.1	42.8	47.8	49.9	50	54.7	

*Only sites in South Africa

NR = not recorded

[#]p-values derived from logistic regression of binary dependent variable with programme year as an independent variable

CHAPTER 3: SYNOPSIS

3.1 Introduction

The papers included in this dissertation include data from children initiating ART over a period of more than ten years (1999 – 2010). This has been a time of rapid expansion and change not only of HIV care and treatment programmes for children, but also PMTCT programmes, which impact on the burden and nature of paediatric HIV. Programmes have had to adapt rapidly and frequently both to increase their capacity as well as to incorporate guideline changes in response to new and emerging evidence of more effective and safer treatment strategies.[20-22,33,129,153] The papers included in this dissertation reflect this evolution in and relationship between WHO and country level guidelines, HIV care and treatment programmes for children, and characteristics and outcomes of children enrolled in these programmes. The literature review paper and two of the analyses are focused on evaluating the outcomes and effectiveness of ART programmes in South Africa in order to inform future programme and guideline development and compare outcomes across different settings. Three analyses focus on strategies for monitoring treatment effectiveness and associations with treatment failure. The last analysis examines ART scale-up for children in terms of changes in characteristics of children at ART initiation in responses to guideline changes.

In order to avoid repetition, comments from the discussion sections of the published papers will not be repeated in this synopsis. Rather, the synopsis will focus on issues raised when considering the papers as a combined body of work in relation to the objectives of the dissertation and in the context of other relevant publications in the field of paediatric ART in resource-limited settings.

3.2 Survival and related outcomes and their determinants.

Mortality and retention in care reported from paediatric ART cohorts

There are now many paediatric ART cohort studies from a range of settings across Africa that have found good outcomes on ART as demonstrated in the published literature review and in the literature review section of this dissertation.[13,154] However, the collaborative South African cohort study included in this thesis remains one of the largest cohorts published from a single country setting representing a substantial percentage of all children in the national programme at the time.[12,155] Uniquely the Malawi national programme has recently reported mortality and LTFU outcomes at 12 months on ART for all of the nearly 10,000 children started on ART between 2004 and 2007 using routine monitoring data.[155]

We reported on outcomes for up to three years after ART initiation which, in contrast to adult studies,[156,157] is still unusual for any paediatric cohort analysis from a developing country setting.[8,12] The finding of mortality at three years of 7.7% and retention in care of 81.4% compares favourably with other studies of pediatric ART from resource-limited settings, but is substantially higher than mortality reported from developed country settings.[12,13,18,27] The large Malawi national cohort reported a mortality rate during the first three months on ART of 24.3 per 100 child years and 5.9 per 100 child years during months four to twelve on ART.[155]

Generalizability of paediatric ART outcomes and their determinants across different resource-limited settings

The South African data reported in the paper describing outcomes of the national programme was included in a multiregional IeDEA analysis of 13,611 children that also included data from Asia, West and East Africa as well as other Southern African countries.[158] By 18 months after ART initiation 5.7% of children had died, 12.3% were lost to follow-up, and

8.6% had transferred to another clinic.[158] Mortality in Asia, Southern and East Africa was similar and lower than in West Africa after adjusting for patient age and disease severity as well as programme characteristics.[158] Probability of LTFU was similar in Asia and Southern Africa and lower than for children in East and West Africa.[158]

A large number of paediatric cohort analyses, including analyses of data from more than one region like the multiregional IeDEA analysis, describe associations of patient characteristics at ART initiation with subsequent mortality.[7,8,10-13,16,18,24,49,155,158] The multiregional IeDEA analysis found that individual child characteristics of age <24 months, WHO Stage IV disease and CD4% <10 were independently associated with poorer survival. In the study of ART outcomes in South Africa, young age, all markers of disease severity (low weight-for-age z-score, high viral load, severe immune suppression, WHO Stage III/IV disease and anaemia) were all independently associated with mortality.[145] Across studies, reported associations are similar, but not exactly the same due to differences in the patient characteristics and settings of each study. This limits comparability of outcomes across programmes. The prognostic model of mortality on ART, however, uses cross-validation across the different regions to identify a model of associations of baseline characteristics with mortality that is generalizable. It also provides absolute predictions of mortality associated with particular child characteristics as has been done in adults.[142,159,160] The finding that most children fall into the group with the good prognosis concurs with the South African paediatric ART outcomes paper as well as other studies from resource-limited settings that show low mortality on ART.[145]

The absolute predictions of mortality that are generalizable across settings are useful for prognosis both at individual level and for programme planning, as well as for comparing outcomes of different programmes. Using a previously collected dataset from many of the same cohorts, we have shown that adjusting for child characteristics at baseline considerably

attenuates the between-programme heterogeneity in mortality outcomes, however the choice of characteristics adjusted for in this analysis were not based on a generalizable model.[24] The large differences in child characteristics of different programmes reported in the literature review and the prognostic model paper highlights the need for a robust generalizable model of mortality.

Association between age and mortality

A striking finding of the paediatric prognostic model was that it compared so well with the adult model for resource-limited settings and actually had higher R^2 and C-statistics.[142] Most studies, including the Southern African outcomes studies included in this thesis, have identified young age at ART initiation as strongly predicting mortality in children.[145,148] The good discrimination and agreement of predicted and observed outcomes in the paediatric prognostic model are ascribed to this powerful prognostic value of age in a setting where children have to "wait" from time of infection (usually perinatally) until particular disease severity criteria are met, before they become eligible for ART.[20] In this context, the age at which a child starts therapy is a proxy for the severity of disease and speed of progression, and may be a more accurate measure of disease progression than other laboratory or clinical measures. The equivalent measure of disease progression in adults is frequently not possible to measure as the timing of infection is often unknown.

With universal ART for all children less than two years of age, and even less than five years of age as currently recommended in South Africa[161,162] and contemplated for WHO 2013 guidelines, assessment of disease severity is not required to determine eligibility. For prognostic purposes, programme planning and comparing the outcomes of different programmes, it may be useful to continue to record and measure a child's age and low cost markers of disease characteristics at ART initiation, however. Nevertheless, as noted in the

paper, new models will need to be developed for children starting ART before the onset of severe disease, as there were insufficient children in our dataset without severe disease to determine meaningful differences in mortality associated with different disease characteristics within the less severe disease spectrum.

Outcome ascertainment

As highlighted in the literature review, however, interpretation and comparison of mortality estimates across settings even after adjustment for patient characteristics at ART initiation, may be difficult due to differences in the accuracy of outcome ascertainment when LTFU is high. In the multiregional IeDEA analysis the crude estimate of LTFU by 18 months after ART initiation was >15% in two regions.[158] As mentioned in the literature review, the few tracing studies in children show that mortality among children on ART who become LTFU may be up to 50%.[116,117] Possible under-ascertainment of mortality in those LTFU/transferred was highlighted as a limitation in the prognostic model study – children transferred/LTFU within six months of ART start were excluded as early mortality on ART is high[12,155] and the risk of outcome misclassification was likely to be highest in this group.[118] The sensitivity analyses demonstrated that mortality at the programme level was indeed affected by assumptions about mortality in this group. A further limitation of the prognostic model is that it is restricted to predictions during the first year on ART. As patients remain on therapy for longer, it will be important to develop models that predict longer term outcomes.[160] For this, good outcome ascertainment in those LTFU/transferred will continue to be important in order to get accurate predictions of mortality. This will enable calculating more accurate predictions of mortality as well as calculating the life expectancy on ART in children as has been done in adults.[163]

Improving estimates of mortality in cohort studies

In South Africa, linkage of HIV cohort patient data to the death registry using the national identification number to improve mortality ascertainment has been done in adults with high sensitivity and specificity for known deaths.[156,164] Using this data in the Khayelitsha adult cohort, about one third of patients LTFU were found to have died, and mortality estimates at five years increased from 15.5% based on facility-level data to 23.4% when correcting for under-ascertained mortality.[156] This approach has been shown to be feasible for children with results very similar to those of adults. In a study of approximately 3,000 children initiating ART in four provinces in South Africa, nearly 50% of children LTFU had a valid national identification number, and one third of these had died according to the national registry.[165] While mortality probability by two years based on deaths recorded in facility-level data was 3.9%, this increased to 6.1% when correcting for the unascertained deaths.[165]

Data from linkage to death registries or tracing studies is, however, frequently unavailable in resource-limited settings. Nevertheless, it may be possible to adjust estimates of mortality at the programme level using a nomogram method based on results of tracing studies.[24,110,111] Although only adult tracing studies were used in developing the nomogram, the finding of similar mortality in adult and paediatric patients LTFU when linking to the South African death registry, supports its applicability to paediatric programmes. The nomogram approach to adjusting mortality estimates has been applied in an analysis of 8,225 children that included the South African data from this thesis as well as data from other Southern African countries. Estimated probability of dying by one year was 4.5% in children remaining in care, but nearly doubled to 8.7% when adjusted for the likely mortality in children LTFU.

Temporal trends in mortality, LTFU and retention in care

In the South African programme outcomes paper LTFU increased from 2.2% in those commencing ART prior to 2006 to 8.2% for those commencing in later years.[145] Under-ascertainment of mortality with increasing LTFU in later programme years has been seen in adult studies from South African cohorts[43,156,166] and in our study is one possible contributory explanation for the apparent protective effect on mortality of starting ART in later years. The major reason postulated for increasing LTFU is increasing patient numbers putting pressure on services at the same facility and limiting ability to trace patients after missed appointments.[46,166] Encouragingly, in an analysis combining data from a number of facilities in four provinces in South Africa Fatti *et al.*[165] showed no difference in corrected mortality and true LTFU between annual enrolment cohorts after adjusting for patient characteristics at ART initiation and correcting mortality for unascertained deaths. This may be because, in the study by Fatti *et al.*,[165] the increasing numbers of children starting ART in later programme years came from increasing numbers of new facilities starting children on ART, rather than the increasing cohort size at the same clinics in our and other studies, supporting decentralization of care.[145]

Impact of transfers and decentralization of care on outcomes of pediatric ART

Both the prognostic model and South African outcomes papers reported very high rates of transfer out from tertiary care sites in the Western cape Province of South Africa, with nearly 50% of the cohort being transferred to primary care within two years of ART initiation.[145] At the time, this practice was fairly unique to the Western Cape paediatric ART program[4] but has now become much more widespread in both adult and pediatric programs.[157,167] Recently, pediatric programs in other provinces have started decentralizing care to facilities closest to the patient's home, and large externally funded adult and pediatric programmes based at

hospitals have transferred patients to primary health care facilities due to reductions in external funding streams for hospital-based care.[168] There has been little research in children or adults on whether patients successfully transfer to their new treatment site and the outcomes of patients transferred.[169,170] In Malawi, 92% of patients transferred from Mzuzu Central Hospital to health facilities nearer their homes were traced as having successfully enrolled at the new facility at a median of 1.3 months after transferring out.[169] Survival probability was reported to be higher in patients transferred, supporting decentralization, however this was not adjusted for the less severe clinical disease in the transferring patients.[169]

Similarly, comparisons of children receiving ART at different level of care facilities have yielded conflicting results due to the difficulty of adequately adjusting for disease severity characteristics and differential LTFU. In the Western Cape province retention in care was lower in children treated at academic and regional hospitals compared to district hospitals and primary care facilities, however this difference was ascribed to unmeasured/unrecorded differences in patient characteristics for which adjustment could not be done.[45] In Malawi, patients treated at either central or rural hospitals had lower mortality but higher LTFU than those treated at district hospitals, while those treated at health centres experienced both lower mortality and lower LTFU compared to those treated at central and district hospitals.[155] When comparing outcomes between urban and rural children and rural children accessing care at urban facilities (rural/urban), mortality was found to be highest in rural children, but LTFU was greatest in rural/urban children who also experienced the poorest virological suppression, suggesting that there are adherence and retention challenges when children receive treatment far from their home.[59,92,171,172] These results support decentralization of paediatric ART to primary care facilities near the patients home, however research on the outcomes of children transferring between facilities is needed.

Effectiveness of ART

Despite concerns regarding outcome ascertainment and notwithstanding the impact of level of care on ART outcomes, the South African outcomes and prognostic model papers both highlight good survival on ART especially when compared with expected outcomes based on data from the pre-ART era.[70] Like other studies, the South African outcomes paper also showed good retention in care, immunological, virological and growth response, although anthropometric and laboratory measures only in patients remaining in care are affected by selection bias.[127,152,173-183] However, we did not analyse pre-ART data, compare pre-ART and on-ART outcomes or attempt to demonstrate a causal link between ART and the positive outcomes reported. A recent analysis of 790 HIV-infected children in the Democratic Republic of the Congo (DRC) used marginal structural models to estimate the effect of ART on survival, adjusting for time-dependent confounders (e.g. CD4) that influence both whether patients received the exposure (ART), and experience the outcome (death), and are themselves affected by the exposure.[123,184,185] This analysis found a 75% reduction in mortality (95% CI: 0.06 – 0.95) when comparing ART with no ART.[185]

Timing of ART initiation in children greater than one year of age

As the study period for DRC analysis ended in August 2010, most data would have been collected prior to the WHO 2010 guidelines, so the effect estimate of ART reflects the mortality benefit when starting ART in children with severe clinical or immunological disease, but does not address the optimal timing of ART initiation in terms of the mortality benefit associated with starting ART at higher CD4 thresholds. A causal modelling analysis of the effect of ART on CD4 recovery using the same data, however, found that recovery was slower in children with lower baseline CD4 percentages supporting earlier initiation of paediatric ART.[186] The CHER trial[33] established the substantial mortality benefit of early ART initiation irrespective of CD4 criteria or clinical disease severity in infants; however the

optimal timing of ART initiation in older children remains unclear.[187-189] The Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) RCT found no difference in AIDS-free survival, Centre for Disease Control (CDC) Stage B or C events, rate of immune response or neurodevelopmental outcomes when starting children aged 1-12 years on ART immediately compared to deferring until WHO 2006 treatment initiation criteria were met.[190-192] However the study was underpowered to detect a mortality difference due to the lower than expected mortality and occurrence of new AIDS events in the study.[189] In addition, it only included a small number of children in the 1-5 year age group in whom disease progression would be expected to be most rapid and the benefits of early ART are likely to be greatest.[188,192] There may be a role to use cohort data to examine the mortality benefit of starting ART at different CD4 thresholds in this age group as has been done for adults.[193-195]

3.3 Measuring treatment success in patients retained in care and determinants of virological failure

Optimal monitoring of children on ART

There has been much debate on optimal monitoring strategies for resource-limited settings and a number of RCTs and cost effectiveness analyses have examined different strategies for measuring treatment success in patients on ART.[37,135,196,197] This is especially important for children where treatment options are limited.[36] Children should remain on first-line for as long as it is effective, but accumulation of resistance mutations that might limit the success of subsequent therapy should also be avoided.[134,180]

Diagnostic accuracy of immunological criteria for identifying confirmed virological failure

In a setting with access to 6-monthly HIV-RNA monitoring, we found that one in five children would meet virological failure (VF) criteria by three years on ART.[146] However, routine HIV-RNA measurement is expensive and remains inaccessible in many settings. A key question is therefore whether it is possible to identify these children without routine HIV-RNA monitoring. A number of studies have now reported similar results to our studies of diagnostic accuracy regarding the poor ability of both clinical and immunological criteria to diagnose VF.[67,144,147,152,180,198] Both of our studies on diagnostic accuracy are the biggest to compare HIV-RNA and CD4 measures and the only studies to do this continuously for up to three years with failure diagnosis based on a confirmed elevated viral load.[144,147] Comparison of immunological criteria with a VF diagnosis based on a single elevated HIV-RNA measurement over-estimates PPV as a substantial proportion of patients resuppress on subsequent measurement.[199] In our paper on TVL, even among children meeting immunological failure (IF) definitions, a small but important number resuppress after a single elevated viral load.[147]

Effectiveness and cost-effectiveness of CD4 and HIV-RNA monitoring in reducing mortality

While clinical and immunological criteria are poor at identifying VF, the impact of this on mortality may be limited. The Antiretroviral Research for Watoto (ARROW) trial in children on NNRTI-based first-line recently reported similar results to the Development of AntiRetroviral Therapy in Africa (DART) trial in adults showing a small risk difference in mortality of patients randomized to laboratory monitoring (CD4 measurements but not HIV-RNA) compared to clinically driven monitoring.[200,201] However the cost-effectiveness of expanding ART coverage was deemed much higher than the addition of CD4

monitoring.[202,203] There has been limited RCT evaluation of HIV-RNA monitoring; lower mortality/new AIDS events were found in adults randomized to either clinical+CD4 or clinical+CD4+HIV-RNA monitoring, compared to those monitored clinically only, but there was no difference in the first two monitoring arms.[204]

Cost effectiveness analyses of different monitoring strategies have mostly focused on adults and have yielded conflicting results due to differences in the strategies evaluated and modelling scenarios.[197,205-211] The only analysis in children based on a cohort on NNRTI-based first line reported the optimal frequency of HIV-RNA monitoring to be annual, after a single screen at 6 months.[210] Compared with no HIV-RNA monitoring, the optimal strategy reduced total person-years of VF by 77%.[210] However the costs of such monitoring and second-line ART when needed would approximately triple current treatment costs.[210] The incremental cost per quality adjusted life year gained using optimal monitoring was estimated as US$ 68,084 when including costs of ART and US$ 7,224 without ART costs.[210] The estimated cost attributed to preventing one year of VF was US$ 3393 and US$ 359 with and without ART costs respectively.[210]

Modest mortality benefits associated with HIV-RNA monitoring in comparison to expanding ART coverage are perhaps not surprising. While remaining on a failing NNRTI-based first-line regimen is associated with rapid and early accumulation of NNRTI-resistance mutations as well as TAMS,[152,173,212] there is limited evidence in children that early switching to second-line confers mortality or morbidity benefit.[212] More than 80% of Ugandan children suppressed on LPV/r-based second-line after failing first-line NNRTI-based therapy with extensive resistance.[213] A systematic review found that in adult patients on NNRTI-based therapy, HIV-RNA needs to be measured three-monthly to avoid the development of resistance mutations.[214] This may not currently be a realistic in resource-limited settings, and a more reasonable approach may be the WHO 2.0 strategy[215] that aims to use drugs with less

monitoring requirements and first and second-line regimens with non-overlapping resistance profiles. Wider availability of integrase inhibitors for children could ensure less overlap of resistance profiles.

Other roles of HIV-RNA monitoring

HIV-RNA monitoring may nevertheless be valuable where it can be made available, irrespective of whether it confers mortality benefit. Our finding that one in five patients still in care by three years of therapy would fulfil the criteria for a diagnosis of VF according to WHO 2010 criteria[22] is extremely useful for programme planning and identifying children needing more intensive review of their treatment, even though not all of these children may require or benefit from second-line therapy. We did not do resistance testing in children with VF, however it is likely that not all of these children have resistance and need second-line ART, especially in the context of LPV/r-based first line therapy where development of resistance is unusual.[141,216,217] Further, the finding that a notable proportion of those with VF showed no virological response to treatment may indicate ongoing poor adherence, rather than true treatment failure, and highlights the difficulty of distinguishing between non-adherence and failure in children on LPV/r-based ART.

Despite these differences in interpreting a VF diagnosis depending on the first-line therapy used, the paper highlights that by three years, 20% of children will need some sort of intervention, whether adherence support, regimen simplification to more adherence-friendly drugs or change to second-line therapy, while the remaining children experience a relatively uncomplicated course in terms of virologic response to treatment. Indeed, in adults on NNRTI-based therapy, it has been argued that at the 6-12 months frequency that HIV-RNA monitoring is currently implemented when available in resource-limiting settings, its major role is to detect non-adherence early enough to intervene and resuppress.[197] In adults the level

of viraemia has been shown to indicate whether the patient is likely to be non-adherent or truly failing therapy.[135,136,218,219] Given that resistance to LPV/r is rare, the major role of HIV-RNA monitoring in children, especially those on PI-based therapy as included in our studies, may also be as an "adherence test". Despite its current cost, such an "adherence test" is very useful in children where the best self-report measure of adherence is by proxy of the caregiver and has been shown to correlate poorly with virological outcomes. Volumetric measurement of returned syrups is cumbersome and may be difficult to interpret due to spitting, spillage and vomiting of medication.[172,220,221] Using HIV-RNA monitoring to identify the 80% of children without VF may also be useful in determining the level of care needed and facilitating decentralization to primary care. A further benefit of HIV-RNA monitoring in resource-limited settings is reducing transmission of resistant virus.[222] This is an important consideration in perinatally infected adolescents who may have been exposed to many years of ART by the time they become sexually active.

Strategies for HIV-RNA monitoring in resource limited settings

Given these non-mortality benefits of HIV-RNA monitoring, there may be a role for innovative monitoring approaches in resource-limited settings that are less costly. These include pooled HIV-RNA measurements on pre-selected patients with a low pre-test probability of having an unsuppressed HIV-RNA measurement, different monitoring frequencies, qualitative point of care tests based on different HIV-RNA thresholds shown to be associated with poor adherence or true VF and TVL strategies.[197,223-227] For instance, a strategy of pooled HIV-RNA measurement on patients with a low pre-test probability of VF resulted in 30-60% fewer tests, thus lowering the cost of HIV-RNA monitoring.[223] This approach may be more difficult to implement in children where the probability of an unsuppressed HIV-RNA measurement is higher than in adults. Indeed, there has been limited evaluation of these approaches especially in children. For example, the cost effectiveness of a

TVL monitoring strategy has only been evaluated in adults, but was found to be the most cost-effective monitoring strategy, with an incremental cost-effectiveness ratio similar to that of ART initiation at higher CD4 thresholds.[207] The analysis of TVL included in this thesis shows substantial improvement in PPV for diagnosing VF compared to immunological criteria alone, suggesting that this may also be a useful strategy in children in settings where access to HIV-RNA monitoring remains restricted.

Guidelines for management of patients with VF

To be beneficial, any monitoring strategy needs to be supported by clear guidelines regarding how to manage patients identified as potentially failing therapy. We found considerable between-site heterogeneity in switching practices, with a large proportion of children not switched to second-line therapy or switched only after a long period.[146] South African 2010 and 2013 draft paediatric HIV guidelines[162,228] are much clearer regarding management of a child with unsuppressed HIV-RNA. Recommendations include earlier repeat testing following HIV-RNA >1000 copies/ml, and lower thresholds for switching in children on NNRTI-based regimens or previously exposed to unboosted RTV, where resistance testing is recommended.[141,217,229]

Strategies for optimising the durability of first-line ART and possible alternative approaches in children meeting VF criteria.

Given the large number of children that may need some sort of treatment intervention, and the few alternative drugs, especially for PMTCT-exposed children initiating LPV/r-based first-line therapy, evaluating strategies that may delay the development of treatment failure, such as temporary treatment interruptions, is warranted. Results regarding treatment interruptions are conflicting: The CHER study found that in children who received ART from early infancy and then interrupted at two years of age, one-third of children had no clinical indication for restarting by the end of follow-up at five years of age,[230] however this approach

seemed less successful in a smaller study where ART was started later in infancy.[231] The Paediatric European Network for Treatment of AIDS (PENTA) trial of planned treatment interruptions in older children (median age of nine years and duration on ART of six years when randomized to interrupt or continue therapy) showed no serious adverse clinical outcomes in children that interrupted therapy.[232,233] This is in contrast to findings from adult studies.[234] The PENTA study found that treatment interruptions were acceptable to patients and carers, however some considered the need for more clinic visits during the interruption to be a problem.[235] Indeed, the need for more intensive clinical and laboratory monitoring of children during interruptions may be a barrier to implementing this strategy in resource-limited settings where facilities are already overburdened and access to laboratory testing is poor.

Monotherapy with 3TC in children with the M184V mutation during periods where there are barriers to adherence may also be a reasonable approach.[236] In a longitudinal US-based cohort it was recently reported that by 12 months after a VF diagnosis (confirmed HIV-RNA >1000 copies/ml), 73% of children remained on their failing first-line regimen, and 5% were changed to mono- or dual therapy regimens such as 3TC monotherapy.[236] The outcomes of this strategy still need to be evaluated, however.

Higher risk of VF associated with NVP-based regimens

We found that NVP was associated with an increased risk of VF in comparison to EFV- or LPV/r-based regimens and this effect was independent of PMTCT exposure.[146] Worse virological outcomes on NVP compared to LPV/r or EFV have been reported from other paediatric ART cohorts[63,131,180] as well as from adult studies.[237] The finding of better virological response to LPV/r compared to NVP irrespective of prior exposure to NVP for PMTCT has now been confirmed by the P1060 RCT.[129,130] P1060 also found that toxicity

was more common with NVP than LPV/r (hazard ratio: 3.00; 95% CI, 1.06 to 8.21) and similar findings have been reported by an analysis of treatment-limiting toxicity of the IeDEA-SA data.[238] Poorer NVP efficacy may be due to the very high viral loads in infants and young children. Agents against which single gene mutations confer resistance such as NVP may be suboptimal in the presence of high viral replication and prolonged time to suppression.[239] In our study of VF, 21% of children had baseline HIV-RNA >1 million copies/ml.[146] While we did not have resistance data in our study, the high frequency of NVP resistance in the NVP arm of P1060, and the rapid accumulation of resistance mutations in children treated with NNRTIs in the PENPACT trial and other cohort studies support this hypothesis.[130,176,212] It has also been postulated that underdosing of NVP may occur during the ramp-up of dosing in the first two weeks of therapy when viral loads in infants are especially high.[130] For this reason as well as simplification of drug administration, ART initiation with full dose NVP has been compared with the ramp-up strategy, but was associated with higher risk of rash.[240] However the authors considered that this may be manageable without interrupting treatment.[240] The baby "cocktail" using a four-drug NVP-containing regimen in infants initiating ART may be another strategy for improving the outcomes in children initiating therapy on NVP-based regimens.[241] A collaborative European cohort study found virological and immunological responses at 12 months after ART initiation in infants on four-drug NNRTI-based regimens to be superior to both three-drug NNRTI-based and PI-based regimens.[241]

Implications for recommended first-line treatment in infants and young children

It is likely that WHO 2013 guidelines will now recommend LPV/r-based first-line ART for all children less than three years old if feasible. However there are a number of challenges to implementing this including the higher cost of LPV/r, lack of FDCs including LPV/r,

difficulty of co-treatment for tuberculosis and unpleasant taste which makes adherence challenging.[187,188] We did not measure adherence in our study, but the high rate of virological non-response may indicate non-adherence in some children. There may be a role for treatment simplification or induction-maintenance strategies in children initiating LPV/r-based therapy such as treatment interruptions described above or changing to NNRTI-based therapy in virologically suppressed children, especially those not previously exposed to PMTCT NVP.[242] The NEVEREST trial examined substitution of NVP for LPV/r in the first-line regimen of virologically suppressed children previously exposed to sdNVP.[243] However, this strategy requires HIV-RNA monitoring both before and after changing therapy which is still not available in most resource-limited settings. In addition, the widespread use of extended NVP prophylaxis in infants for PMTCT, limits the applicability of the NEVEREST findings.

While LPV/r is now available in tablet formulation, tablets are large and cannot be crushed making their administration difficult.[244] There are, however, promising results of a new generic LPV/r sprinkle formulation that has recently been evaluated in Uganda in children aged one to four years.[245] Pharmacokinetic parameters were similar to those of LPV/r syrup with neither formulation resulting in subtherapeutic concentrations.[245] Nevertheless, while carers preferred the sprinkle for storage and transport reasons, nearly 70% rated both syrup and sprinkle formulations as unpleasant, and nearly 20% of carers reported child refusal of the drug in sprinkle formulation.[245]

Limitations: effect of PMTCT exposure and tuberculosis on risk of VF

Like many cohort studies, our study did not have sufficient data to look in detail at the effect of prior PMTCT exposure on VF.[63] However, it is well known that prior exposure to sdNVP is associated with the development of resistance mutations[124,128,216,246-251] and cohort studies

as well as the P1060 cohort trial have demonstrated an increased risk of VF.[129,252,253] Resistance has also been reported in children infected despite maternal triple ART for PMTCT,[254,255] however the impact of this on subsequent virological response to treatment is unknown.

We also had insufficient data on co-treatment for tuberculosis to determine its effect on VF. Other studies have reported lower probability of virological suppression and higher risk of rebound only among children on PI-based first-line regimens co-treated for tuberculosis or experiencing incident IRIS.[41,98,256,257] Frohoff *et al*. [257] found that amongst children on PI-based first-line, virological suppression in children co-treated for tuberculosis was only lower than for children without tuberculosis among those treated with double-dose LPV/r or RTV alone, but not among those treated with RTV-boosted LPV/r. In contrast, Reitz *et al*.[41] found poorer virological outcomes in co-treated children on PI-based therapy irrespective of the treatment modification used. Poorer virological outcomes in children treated with RTV were also found in our study and it was not possible to determine whether this was due to RTV itself or tuberculosis.[146] However, the development of resistance mutations in children treated with unboosted RTV, in contrast to the rarity of resistance in children treated with LPV/r, has been established.[141,216,217,229]

Role of cohort studies in monitoring the safety and effectives of ART

The finding of increased risk of VF in children treated with NVP compared to LPV/r in our and other cohort studies, highlights the important role for well conducted and appropriately analysed cohort studies in rapidly generating effectiveness and safety data. Due to the large size and lack of exclusion criteria of cohort studies, in some circumstances their results may be more generalizable and more applicable to routine care settings than that of RCTs. It has been argued that, if analyzed correctly, cohort studies may be able to answer questions in the

field of comparative effectiveness research that do not lend themselves to assessment in standard analyses of RCTs.[258-260] Comparative effectiveness research (CER) is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or improve the delivery of care.[261] When applied to a chronic condition such as HIV, RCTs have been very successful in showing that ART is beneficial, however a number of key questions such as what to start, when to start, when and how to monitor and when to switch remain unanswered.[22] For each of these questions there are a range of possible strategies with potentially very wide variation in effectiveness and safety. While RCTs are the best method of assessing the effectiveness of one-time treatments, they are a less well suited to examining the effectiveness and safety of long term clinical strategies.[123,260]

Cohort studies may be especially important in the rapidly changing field of CER to inform HIV care and treatment guidelines and there are a number of examples where evidence has emerged from cohort studies rather than RCTs, leading to guideline changes. For example, stavudine-associated lactic acidosis was identified by cohort studies[262-264] and not in the initial RCTs of the drug which were mainly conducted in North America in populations where the prevalence of risk factors associated with developing this condition (female sex, overweight) were low.[260,262] One of the IeDEA-SA paediatric cohorts has recently demonstrated a decline in probability of virological suppression at 6 and 12 months co-incident with the change from d4T to ABC based first-line therapy.[265] While secular trends cannot be excluded as the cause of this finding, it is plausible that it may be due to lower efficacy of ABC especially in patients with higher viral loads.[266,267] Cohort studies may be particularly important for children where conducting RCTs is more challenging and many current treatment guidelines are based on limited or poor quality evidence.[22] They may also

be particularly useful in monitoring safety and effectiveness after guideline changes as illustrated by these two examples.

3.4 Monitoring the scale up of ART for children through temporal trends in characteristics at ART initiation

Improvement in disease severity characteristics at ART initiation

The paper on temporal trends at ART initiation demonstrates successful scale up of ART in that in recent years increasing numbers of children have started therapy, children are initiating ART with less severe disease and the proportion of infants starting ART is increasing. However, even during 2010, a substantial number of children still initiated ART with advanced disease. One of the reasons for slow improvements in characteristics at ART start may in fact reflect successful expansion of access to ART as there may be a reduction over time in the survival bias when examining patients initiating therapy. In later years, as experience with paediatric ART increased and time from diagnosis to ART initiation decreased, children may have been initiated on ART who previously would have died before ART start. This hypothesis is supported by an analysis of adults from first HIV visit to ART initiation in the Free State province of South Africa, with the two competing outcomes of time to ART initiation or death prior to ART start. Compared to patients with CD4 of 100-200 cells/mm^3, those in the lowest CD4 category (<25 cells/mm^3) were 35% less likely to start ART because they were three times more likely to die before ART initiation.[268] The risk of dying before ART initiation may be even higher for infants and young children where disease progression is very rapid and barriers to ART initiation may be greater than in adults.[5,36,37,70,71,82] Two years after eligibility in the Free State pre-ART mortality was 26% in comparison to mortality of 52% by one year of age in perinatally infected infants.[82,83] In

South Africa, between 1997 and 2002 before widespread availability of PMTCT or paediatric ART, an increasing peak in infant mortality was noted at two to three months of age, which was most likely due to HIV, highlighting the rapid disease progression and high early mortality associated with paediatric HIV infection.[269] Consequently, one of the major barriers to early infant ART even where PCR testing is widely available and implemented at six weeks of age, is the optimal timing of testing. A two-stage testing approach at birth and 10-14 weeks of age could avert rapid disease progression and early mortality in perinatally infected infants.[270]

Temporal trends in age at ART initiation

As was found by a previous South African analysis of temporal trends in characteristics at ART start, there were growing numbers of both infants and older children at ART initiation.[165] These results concur with predictions from a South African model of paediatric HIV. By 2020, with more effective and better coverage of PMTCT resulting in fewer new infant infections and hence a shift to more ART initiation in older long-term survivors, as well as children living longer on ART, the burden of paediatric HIV disease is predicted to shift towards older children.[271] The mean age of children either on ART or ART-eligible (based on WHO 2006 criteria) was estimated to have increased from 3.3 years in 2000 to 7.2 years in 2010, and is predicted to increase further to 8.1 years by 2020.[271] In contrast, in our analysis the median age declined as we only looked at characteristics at ART start, and ART initiation in most of the IeDEA-SA cohorts by the end of 2010 included universal ART for all infants less than one year of age, rather than the more restrictive WHO 2006 guidelines used in the model-based analysis. Like our analysis, most papers only report on characteristics at ART start, however examining the changing age structure and disease characteristics in children remaining in care is also important to ensure that programmes continue to be focused on the needs of children receiving treatment.[272]

Diagnosis and linkage to care of HIV-infected infants

Our analysis comments on the importance of early diagnosis and linkage to care in ensuring that infants start ART before disease progression, but does not actually include data from the pre-ART period. In a meta-analysis of retention in care between HIV diagnosis and starting ART, including mostly older children, 63-89% of children identified as HIV-infected were assessed for ART eligibility and 39-99% of eligible children started ART.[273] Estimates of pre-ART mortality and LTFU ranged from 3-46% and 0-37%, but were only reported by a few studies.[48,53,58,69,116,185] None of the studies reviewed examined retention in care in those known to be HIV-exposed from birth through diagnosis to ART initiation in the era of universal ART, where there is no eligibility assessment step. However a high proportion of known HIV-exposed infants do not return for PCR testing,[274-276] and we know that disease progression and mortality in this period is rapid especially in infants infected *in utero*.[33,72,270]

Measuring paediatric ART coverage

Our analysis demonstrates increasing numbers of children on ART that match the findings of increased ART coverage.[2,32] Johnson and Boulle[277] highlight the difficulties in interpreting coverage statistics that are highly sensitive to changes in eligibility criteria[235] as well as programme duration, whereby longer running programmes will have an increasing number of patients contributing to both the numerator and denominator of the coverage metric, with little influence of recent programme performance.[277] They propose an additional measure of recent programme performance, the enrolment ratio, which is the ratio between the number of children initiating ART in a particular time period and the number of new infections in children <24 months of age in the same period.[277] The enrolment ratio needs to be considered alongside coverage figures, as, if there is a large coverage backlog, the enrolment ratio may be greater than one.[277] This is particularly important in children where coverage backlogs in

many countries are large.[1] Even using coverage and enrolment ratio, poor programme performance in terms of rapidly initiating ART in infants where mortality benefit is the greatest can easily be missed as enrolment ratios may be much greater than one due to the backlog of older children not yet on ART. Expansion of universal ART to all children less than five years of age as has been adopted in South Africa[161,162] and is likely to be recommended in WHO 2013 guidelines will simplify programmes and may therefore accelerate early ART initiation in younger children as well. This is one of the reasons provided for the change in South African guidelines.[161,162] However it may muddy the waters when interpreting coverage statistics even further. Coverage may improve as programmes initiate ART in children already in HIV care now eligible for treatment under new guidelines, without any increase in diagnosis and early ART initiation in infants. Aiming for higher coverage of all children under five years may even occur at the expense of investing resources in ensuring early diagnosis and treatment in infants where there is a known mortality benefit. In Uganda, the main ART eligibility criterion that did not lead to ART initiation was being <12 months of age.[235] For the most part, expansion of ART initiation to patients without immune suppression is associated with modest mortality benefits[193,278,279] and the rationale for extending universal ART to all children less than five years of age is based on programmatic simplification, with no proven mortality reduction.[191] In contrast, universal ART for all infants less than one year of age has large proven mortality benefit[33] and it is important to directly monitor the extent to which this goal is being achieved.

Other areas of observational HIV cohort research important for understanding and improving paediatric ART scale-up

This thesis has used analyses of the IeDEA-SA combined dataset from paediatric observational cohorts to reflect on a number of areas critical to understanding and improving HIV care and treatment programmes for children. These include treatment outcomes,

particularly mortality and its determinants, the measurement of treatment effectiveness in children in resource-limited settings, determinants of treatment failure, the role of HIV cohort research in monitoring the safety and effectiveness of different ART regimens as well as initiation and monitoring strategies, and the extent of successful expansion of access to ART, especially in response to revision of treatment guidelines.

There are, however, a number of other key areas of cohort research not addressed by this thesis that are important for informing successful paediatric ART programmes. These include studies of comorbidities such as IRIS, malignancy,[280] opportunistic infections and prophylaxis[94,98,99,121,122,256,281-288] as well as adherence to therapy and retention in care,[92,115,117,172,289,290] and the impact of different models of care on these outcomes. In particular, with the increasing age of children in care in ART programmes, it is important to understand the effect of HIV disclosure, as well as different models of transition from paediatric to adolescent and ultimately adult care on adherence and retention in care.[291,292] Ways of successfully integrating such models of care into existing health services in a context of limited resource need to be examined. For example, while task-shifting has been widely proposed as a means to expand access to ART and nurse initiation and management of ART in adults has been shown to be non-inferior to that of doctors, these approaches have not been extensively studied in children.[293-298] Similarly, there may be a role for adherence clubs or community-based care in children and adolescents, but these have not been evaluated in this population.[299-302] Paediatric ART cohorts may be well positioned to implement and evaluate some of these strategies.

3.7 Conclusions

This thesis has analysed outcomes on ART both within South Africa and across the Southern African region, with a focus on mortality and VF. It has reviewed monitoring strategies for identifying children with VF needing adherence interventions or second line therapy in the absence of access to routine HIV-RNA monitoring. Lastly it has reviewed the evolution in HIV programmes in relation to changing WHO and national guidelines by examining changes in child characteristics at ART start since initiation through three iterations of WHO guidelines.

The first major contribution of the thesis is to demonstrate the good outcomes for up to three years on ART in cohorts representing a substantial proportion of the South African national ART programme, supported by good compliance with monitoring guidelines. The prognostic model extends the finding of good survival outcomes on ART to programmes across the region and provides estimates of absolute mortality risk based on a generalizable model that is reasonably robust to programme heterogeneity.

A second major contribution is to provide estimates for up to three years on ART of confirmed VF in children on both PI- and NNRTI-based therapy, and to demonstrate the poor diagnostic accuracy of non-routine HIV-RNA monitoring strategies for identifying these children. While sensitivity for VF is low, a TVL strategy can reduce switches to second-line therapy in virologically suppressed children with immunological failure.

Thirdly, we demonstrated inferior virological outcomes in children treated with NVP-based compared to LPV/r based first-line therapy, irrespective of PMTCT exposure, a finding which has now been confirmed from RCT data.

Finally, changes in number and characteristics of children at ART initiation from 2005-2010 suggest increasing access to ART in children and provide useful data for designing

programmes that are tailored to the children being treated. The improvements in ensuring earlier access to ART at less severe disease are, however, modest. Future extensions of eligibility will make it increasingly difficult to monitor that very young infants who are at greatest risk of mortality in the absence of ART are prioritised for rapid initiation. This analysis thus highlights the need for integration of services for PMTCT, maternal and child health and paediatric HIV care in order to ensure early diagnosis and ART initiation. As PMTCT coverage and effectiveness increase, it will be important to also integrate research in these areas so that the impact of PMTCT exposure on the outcomes of HIV-infected and the large numbers of HIV exposed uninfected children can be studied, and the interface and pathway between PMTCT, early infant diagnosis and HIV care can be understood and optimized.

The thesis also emphasizes the role of paediatric HIV cohort research in order to answer clinical questions related to treatment strategies and models of care for children on lifelong ART that may be difficult to answer in RCTs. With increasing numbers of adolescents surviving with HIV and exposed to ART for long periods of time, the interaction between pubertal development, the effects of HIV and its treatment needs to be understood.[292] Cohort studies may be well positioned to assess this. It is also important that cohort studies continue to evaluate the effect of guideline changes in eligibility, monitoring and regimen use and provide early evidence of safety and effectiveness outcomes and their determinants in routine care settings.

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APPENDIX:
IeDEA Southern Africa Data Transfer Protocol

IeDEA
International epidemiologic Databases to Evaluate AIDS

Southern Africa

STANDARD PROCEDURE FOR DATA TRANSFER

Version 1.0 / August 2007

Contact: iedea-info@ispm.unibe.ch
www.iedea-sa.org / www.iedea-hiv.org

Contents

Lookup tables

1 Introduction

1.1 General remarks

- This document provides guidance on the preparation of data tables for the transfer of data for the IeDEA Southern Africa Collaboration.
- It is requested that each clinic prepares **ten separate tables** with the new data, as described in detail below. While 6 of these tables should be submitted by all sites, tables 7 -10 will only be applicable to certain sites (see below).
- The tables can be sent in the format that is most convenient for the site, including MS Excel, MS Access, ASCII etc. Please contact the IeDEA data manager if you have any queries.
- **It is appreciated that for some clinics it may be easier to send their data as they stand (for example in Excel) and to leave the data management and preparation of the ten tables to the data centre. This is not a problem, but it is requested that a separate document be included with a list of the variables in the dataset and brief descriptions/definitions.**
- It is accepted that there will be missing data for some patients, and even entire missing tables from some sites who simply do not have that data in electronic format.
- It is requested that for security purposes, data tables be encrypted and compressed with WinZip 9 or higher using the AES encryption algorithm prior to sending. The encryption password (minimum of 10 characters long, including upper/lower case, numbers and special characters) should be communicated to the relevant data centre contact person by fax or by telephone.
- Please ensure that the dataset has been stripped of personal identifying information prior to sending.
- Please include a unique anonymous identifier for each patient (PATIENT) for cross-reference with your own database. It can be the identifier you are using or a special identifier you create for IeDEA Southern Africa. This anonymization key must be maintained by the site under secure conditions.
- Sites treating children should please send the date at which they changed from using the WHO 3-stage clinical staging system to the 4-stage clinical staging system.
- Thank you very much for your contribution to this collaborative project!

1.2 Inclusion criteria for patients

Please include all patients with the following characteristics:

- Documented HIV-1 infection
- Patients in care at the facility for whom the date of first visit at the facility is known exactly.

Notes:

- Where possible, it is intended that data be transferred on HIV-infected patients followed-up at the facility irrespective of whether or not they received highly active antiretroviral therapy (HAART).

- When transferring data just on patients who received HAART, it is preferable to include patients irrespective of whether or not they were exposed to antiretrovirals before the recorded HAART start date. In other words treatment-naïve and treatment-experienced patients are included.
- Sites should send all information on all patients (adults and/or children) in a single dataset. For adult patients (those whose **first visit at your facility was after their 16th birthday**) the paediatric specific fields (highlighted in blue) do not need to be completed (i.e. enter code 88 – not applicable). Paediatric specific fields must be entered as completely as possible for all patients whose **first visit at your facility is before their 16th birthday** even if their follow-up extends beyond the age of 16 years.
- Some patients will have been in care at another facility prior to commencing care at your facility. These patients should be included in the dataset, noting against the relevant field that they have been transferred in. All treatment and opportunistic infection (OI) history prior to commencing care at the facility should be reconstructed as far as possible and entered in the appropriate tables, with unknown codes for dates of start and end date of OIs/antiretroviral drugs where necessary.

1.3 Dates

- The term baseline will not be used as this creates confusion. We will rather make use of a set of key dates that will be entered into the first table, the **PATIENT** table. These are:

Variable name	Definition of key date
FRSVIS_DMY	Date of first visit at your facility
HIVP_DMY (HIVP_Y (year) and HIVP_M (month) if exact date unknown)	Date of first positive HIV-1 test
HAART_DMY	Date of HAART initiation

- For all fields that require a date, the precise date should be entered in the format dd-mm-yyyy if it is known. If the precise date is not known, the month and year should be entered separately as far as possible in the separate dedicated fields provided for these, and the precise date field should be left blank.
- If month or both the year and month are unknown, the precise date field should be left blank and unknown codes should be entered into the year field (9999) and the month field (99) as appopriate.
- For certain date fields a precise date is obligatory e.g date of first visit at your facility (FRSVIS_DMY) and date of HAART initiation (HAART_DMY). In patients who commenced HAART at another facility, if the precise date of start of HAART cannot be estimated reasonably accurately, the patient should be entered as treatment experienced and the date of first visit at your facility will be regarded as the date of start of HAART.

1.4 Definitions

- HAART is defined as treatment with a combination of at least three drugs from any class or classes.
- "Treatment experienced" is defined as previous exposure to any antiretroviral drug for at least 30 days, **excluding** exposure for prevention of mother to child transmission (PMTCT) or post-exposure prophylaxis (PEP).

1.5 Standard codes

Certain codes will appear repeatedly in a number of lists for coded fields. In this instance, the same codes/coding format will be used in all fields where these codes appear as follows:

Codes	Description
0	No
1	Yes
90	Other
95	Not ascertained/Not collected at this facility
99	Unknown despite attempting ascertainment
88	Not applicable

1.6 Data tables

For each clinic, the following **five** to **ten** data tables or files should be prepared, depending on data availability.

- Tables 1 to 5 are required by all sites.
- Table 6 (LINKAGE DATA) is required only for sites that record information on families
- Table 7 (PREGNANCY) is required only for sites that record information on pregnancy electronically.
- Table 8 (PAR HEALTH) is required only for patients who commence care before their 16th birthday.
- Table 9 (TB) is required only from sites that record detailed information on episodes of tuberculosis electronically.
- Table 10 (TRIAL) is required only for sites where patients may be enrolled on clinical trials or research studies apart from cohort analyses of routinely collected data.
- In addition, a table summarising with information on the overall cohort or "meta-data" for the transfer, should be included with all transfers.

1. **PAT (Patient data)**: A table containing socio-demographic data on patients, clinical characteristics at start of HAART in HAART-treated patients, as well as information on the **outcomes** of patients. One line will correspond to one patient. In other words, each patient will appear only once in this table. We propose that this table is called **PAT**.
2. **LAB (Laboratory data at baseline and follow-up)**: This is a single table containing all laboratory data: CD4, HIV viral load, and all other laboratory tests. One line will

correspond to one laboratory result. In other words, most patient will have multiple records in this table. We propose that this table is called **LAB**.

3. **ART (Antiretroviral treatments)**: A table with the data on all antiretroviral drugs that a patient has received or been exposed to including PMTCT (both exposure to mother as well as infant peri- or post-natal) or post-exposure prophylaxis. This includes treatment received at your facility and at other facilities. The table will contain one line for each separate drug, with different fields for the drug name (code), the prescription start dates and stop dates. Most patients will have numerous records in this table. The drug history of patients who commence care at your facility but have previously been treated at another facility should be reconstructed and entered into this table as far as possible. We propose that this table be called **ART**.
4. **OI (Opportunistic Events):** A table with the information on all opportunistic infections or incident HIV-associated diagnoses. One line will correspond to one clinical event with different fields for the event type (code), the start dates and stop dates. It is anticipated that stop dates will often not be known. In other words, some patients will have more than one record in this table and some may have no records in this table. History of opportunistic events occurring prior to commencing care at your facility should be reconstructed as far as possible. We propose that this table be called **OI**.
5. **VIS (Visit data)**: A table containing information on all clinical visits (including the first visit at your facility). One line will correspond to one visit. Most patients will have more than one record in this table. We propose that this table be called **VIS**.
6. **LINK (Linkage data)**: A table containing information on family members (partners, children and siblings) also receiving HIV care either within your cohort or at another site. All family members receiving HIV care should be included whether they are receiving care at an IeDEA collaborative site or at a non-IeDEA site. One line will correspond to one family member receiving HIV care. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table is called **LINK**.
7. **PREGNANCY (Pregnancy data):** A table containing information on all pregnancies, including spontaneous abortions/miscarriages and terminated pregnancies, and their outcomes. One line will correspond to one pregnancy. Multiple pregnancies will each have a record in the table, with the outcome of the relevant foetus recorded. Some patients will have more than one record in this table, while others (including all males and children less than 10 years) will have no records in this table. We propose that this table be called **PREGNANCY**.
8. **PAR_HEALTH (Parental health):** A table with information on parental health status. This table is only required for sites sending data on patients 15 years old and younger at their first visit to the facility. This table is linked to the visit table, so ideally there is an update on parental health status at every visit. Alternatively, this table should be filled in at least once, either for the first visit at your facility or the date of start of HAART.
9. **TUBERCULOSIS (Tuberculosis data):** A table with information on all episodes of tuberculosis (TB). This table is only for sites that record detailed information on TB episodes. Sites that do not collect detailed information on TB episodes should enter the TB episodes in the OI table. One line will correspond to one TB episode. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table be called **TB**.
10. **TRIAL (Enrolment in trials):** A table with information on any trial or research study (apart from cohort analysis of routinely collected data) on which a patient is enrolled. This table is only for sites running trials or research studies. One line will correspond to one trial/research study on which the patient is enrolled. In other words, some patients will have

more than one record in this table and some may have no records in this table. We propose that this table be called **TRIAL**.

11. **MET (Meta-data):** A table comprising key characteristics of the data that is transferred.

2 Variables to be included in core tables

2.1 Socio-demographic characteristics and outcomes (PAT table)

Table 1 below details the data that should be included in PAT table.

The patient identification variable (PATIENT) must be unique, and it cannot be missing in any of the tables. This field must contain a unique and anonymous patient identifier; the field must NOT contain their name or any other identifying information. It is up to the local collaborator to maintain the key for linking the unique patient identifier with the patient.

Table 1 – Variables to be included in PAT table

Name	Format and definitions	Description
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
FACILITY	Text	Text field identifying particular clinic within cohort, if more than facility within the cohort
BIRTH_DMY	DATE (dd-mm-yyyy)	Date of birth Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
BIRTH_Y	Numeric (for example 1960) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of birth
BIRTH_M	Numeric (for example 8) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of birth
GENDER	Numeric with codes: 1 = Male 2 = Female 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Sex / gender of patient
FRSVIS_DMY	DATE (dd-mm-yyyy)	Date of first visit at facility (Note: This date must be entered exactly)
ENTRY	Numeric with codes (see List 1)	Mode of entry to your facility
ENTRY_OTHER	Text	Details of other mode of entry not listed in List 1
MODE	Numeric with codes (see List 2)	Most probable mode of HIV transmission

HIV_TYPE	Numeric (for example 1) 1 = HIV-1 2 = HIV-2 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Field to distinguish HIV-1 from HIV-2
HIVP_DMY	DATE (dd-mm-yyyy)	Date of first positive HIV test Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
HIVP_Y	Numeric (for example 2001) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of first positive HIV-1 test
HIVP_M	Numeric (for example 8) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of first positive HIV-1 test
HIV_TEST	Numeric with codes (IeDEA SA codes) 1 = Presumptive diagnosis 2 = Serology 3 = PCR 4 = P24 5 = Rapid test 90 = Other 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Type of test used for diagnosis
HAART	Numeric 0 = Never started HAART 1 = Started HAART	Conditional: If 1 then go to HAART_DMY
HAART_DMY	DATE (dd-mm-yyyy)	Date of HAART initiation (minimum 3 drugs together) Note: This date must be entered exactly. If patient commenced HAART at another facility and the exact date is not known, the patient should be entered as "Treatment experienced" in the EXP_Y field below and the first visit at your facility will be used as the start of HAART date.
FHV_STAGE_WHO	Numeric with codes: 1 = Stage I 2 = Stage II 3 = Stage III 4 = Stage IV 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Clinical WHO stage (I to IV) at time of starting HAART (Enter 88 patients who have not commenced HAART)

FHV_SDI_1	Text (for example PCP - see List 3) 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Stage defining illness-1 at time of starting HAART. (Enter 88 patients who have not commenced HAART) Note: At least FHV_S_SDI_1 should be completed in patients commencing HAART; A maximum of 4 stage defining illness can be entered in the 4 fields provided. There is no specific ordering to the entering of stage defining illnesses.
FHV_SDI_2	Text (for example PCP - see List 3) 0 = No further stage defining illness 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Stage defining illness-2 at time of starting HAART. (Enter 88 patients who have not commenced HAART)
FHV_SDI_3	Text (for example PCP - see List 3) 0 = No further stage defining illness 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Stage defining illness-3 at time of starting HAART. (Enter 88 patients who have not commenced HAART)
FHV_SDI_4	Text (for example PCP - see List 3) 0 = No further stage defining illness 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Stage defining illness-4 at time of starting HAART. (Enter 88 patients who have not commenced HAART)
EXP_Y	Numeric with codes: 0 = No (No previous ARV experience) 1 = Yes (Treatment experienced, drug history known and recorded in ART table) 2 = Yes (Treatment experienced, drug history not known) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient is treatment experienced prior to starting HAART (HAART_DMY) ? Experienced = Any ARV drug for at least 30 days before starting HAART (PMTCT regimen and PEP excluded) This should be entered for all patients even those who have not commenced HAART.
MTCT_Y	Numeric with codes: 0 = No (No MTCT exposure) 1 = Yes (MTCT exposed, drug history reconstructed and recorded in ART table) 2 = Yes (MTCT exposed, drug history not reconstructable) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient exposed to MTCT drugs (either mother during pregnancy or infant peri- or post-natally) prior to start of HAART (HAART_DMY)? This should be entered for all patients even those who have not commenced HAART.

PEP_Y	Numeric with codes: 0 = No (No PEP exposure) 1 = Yes (PEP exposed, drug history reconstructed and recorded in ART table) 2 =Yes (PEP exposed, drug history not reconstructable) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient exposed to post-exposure prophylaxis (PEP) drugs prior to start of HAART (HAART_DMY)? This should be entered for all patients even those who have not commenced HAART.
TB_FHV	Numeric with codes 0 = No 1 = Yes 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient was on treatment for TB at start of HAART (HAART_DMY) (Enter 88 patients who have not commenced HAART)
WKS_TB_FHV	Numeric (for example 8) 88=Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Duration in weeks since start of TB treatment when HAART was commenced in patients with TB at start of HAART (Enter 88 for patients who have not commenced HAART or who did not have TB at start of HAART)
PREG_FHV	Numeric with codes 0 = No 1 = Yes 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Pregnant at start of HAART (Enter 88 for men and children <10 years old AND all patients who have not commenced HAART)
LAST_CONTACT_DMY	DATE (dd-mm-yyyy)	Date of last contact Note: This date must be entered exactly.
LAST_CONTACT_T	Numeric with codes (See List 4)	Type of last contact
OUTCOME	Numeric with codes (See List 5)	Outcome including death and loss to follow-up
OUTCOME_DMY	DATE (dd-mm-yyyy)	Date of outcome (Leave blank if outcome is Alive [in care] or Alive [not in care])
OUTCOME_Y	Numeric (e.g. 2004) 8888 = Not applicable or exact date of outcome entered above 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of outcome Enter 8888 for patients who have not died, or if exact date of outcome entered above.

OUTCOME_M	Numeric (e.g.12) 88 = Not applicable or exact date of outcome entered above 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of outcome Enter 88 for patients who have not died, or if exact date of outcome entered above.
DEATH_C1	Numeric with codes (see List 6)	Cause of death : Enter 88 for patients who have not died Note : There are 3 fields for 3 causes of death to be entered in no specific order. If an HIV-related cause of death is recorded, please ensure that the condition is recorded appropriately in the OI table. Nature of contribution of cause: For each cause of death, please characterise the contribution of the specific cause.
DEATH_N1	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	
DEATH_C2	Numeric with codes (see List 6)	
DEATH_N2	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	
DEATH_C3	Numeric with codes (see List 6)	
DEATH_N3	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	
CAREG	Numeric with codes (see List 7)	Primary caregiver at start of HAART (HAART_DMY) (paediatric patients only – enter 88 for adult patients)
DISCL_CG	Numeric with codes (see List 8)	Person informed of the HIV status of the child (paediatric patients only – enter 88 for adult patients)
DISCL_CHILD	Numeric with codes 0 = No 1 = Yes 2 = In process 88 = Not applicable (adult patient) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Was the child informed of his/her status at HAART_DMY? (paediatric patients only - enter 88 for adult patients)

DELIV_M	Numeric with codes 10 = Vaginal, spontaneous 11 = Vaginal, forceps 12 = Vaginal, vacuum 20 = Caesarean section – primary/elective (before onset of labour and rupture of membranes) 21 = Caesarean section – emergency 22 = Caesarean section – type unknown 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Mode of delivery (paediatric patients only - enter 88 for adult patients)
WEIGHT_BIRTH	Numeric (e.g 3.20) 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Weight at birth in kg (paediatric patients only - enter 88 for adult patients)
BRSTFD	Numeric with codes 10 = breastfeeding, exclusive 11 = breast-feeding, exclusivity unknown 12 = mixed feeding 20 = Formula feeding 88 = Not applicable 95 = Not ascertained 99 = Unknown, despite attempting ascertainment	Main infant feeding option after birth (paediatric patients only - enter 88 for adult patients)
BRSTFD_ED	DATE (dd-mm-yy)	Date of cessation of breast feeding if applicable Leave blank if not applicable, child still being breastfed, date not known, or child not breastfed at all.
BRSTFD_EST_DUR	Numeric (e.g. 2) 77 = still breast-feeding, ED unknown 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Estimated duration of breastfeeding in months in children who are exclusively breastfed or mixed fed. (paediatric patients only - enter 88 for adult patients) Enter 88 if child still being breastfed or child not breastfed at all.

List 1 - Codes for mode of entry (ENTRY)
Code source: IeDEA SA codes
Table name: LU :PAT :ENTRY

Codes	Mode of entry
1	PMTCT program
2	Diagnosis testing during hospitalization
3	Diagnosis testing during consultation
4	Orphans programs
5	Family diagnosis
6	TB program
7	General HIV service clinic
8	Self-referral with known diagnosis
90	Other
95	Not ascertained
99	Unknown despite attempting ascertainment

List 2 - Codes for mode of infection (MODE)
*Code source: Based on HICDEP codes; new codes denoted by **
Table name: LU_mode

Codes	Mode of infection
1	Homo/bisexual man
2	Injecting drug user
3	Homo/bisexual man + injecting drug user (1 + 2)
4	Haemophiliac
5	Transfusion, non-haemophilia related
6	Heterosexual contact
7	Heterosexual contact + Injecting drug user (6 + 2)
8	Perinatal
90	Other
95*	Not ascertained
99	Unknown despite attempting ascertainment

List 3 - Disease codes for FHV_SDI (PAT table) and OI_ID (OI table)
*Code source: Based on HICDEP codes; new codes denoted by **
Table name: LU:DIS

Note that this is a common list of HIV-associated conditions for capturing incident opportunistic infections and HIV-associated conditions, as well as stage-defining conditions in adults and children. Where duration or recurrence is required for a condition to be stage defining, the event columns have a zero to exclude them from lookups of incident conditions. Where conditions are not stage defining, the stage-defining columns for children and adults have zeros to exclude them from lookups of stage-defining conditions.

Codes	Description	WHO stage (Adult)	WHO stage (Paed)	Event (Adult)	Event (Paed)	SDI (Adult)	SDI (Paed)
ANGC*	Angular cheilitis	2	2	1	1	1	1
BCGD	BCG disease – disseminated	4	4	1	1	1	1
BCGL*	BCG Lymphadenitis (localised to R axilla)	88	88	1	1	0	0
BCGP*	BCG Pulmonary	88	88	1	1	0	0
BCIR*	Recurrent severe presumed bacterial infection (excluding pneumonia)	4	4	0	0	1	1

BCIS*	Severe presumed bacterial infection – single episode (excluding pneumonia)	88	88	1	1	0	0
BCNE	Bacterial pneumonia, recurrent (>2 episodes within 1 year)	4	3	0	0	1	1
BCNS*	Severe presumed bacterial pneumonia (single episode)	88	88	1	1	0	0
BLD*	Unexplained anaemia (<8g/dl), and or neutropaenia (<500/mm3 – 2; <1000/mm3 - children), and or thrombocytopaenia (<50000/mm3) > 1 month	3	3	0	0	1	1
CANM*	Candidiasis (oral) (outside neonatal period)	3	3	1	1	1	1
CANO	Candidiasis oesophogeal	4	4	1	1	1	1
CANT*	Candidiasis (trachea, bronchi or lungs)	4	4	1	1	1	1
CLD*	Chronic HIV-associated lung disease	88	3	0	1	0	1
CMO*	HIV-associated cardiomyopathy	88	4	1	1	0	1
CMVO	Cytomegalovirus other location (site other than liver, spleen or lymph nodes) (onset at age>1month)	4	4	1	1	1	1
CMVR	Cytomegalovirus (CMV) chorioretinitis (onset at age>1month)	4	4	1	1	1	1
CRCO	Cryptococcosis extrapulmonary	4	4	1	1	1	1
CRSP	Cryptosporidiosis (duration > 1 month)	4	4	0	0	1	1
CRSPS*	Cryptosporidiosis ?	88	88	1	1	0	0
CRVC	Cervical cancer (invasive)	4	88	1	1	1	0
DEM	AIDS dementia complex	4	88	1	0	1	0
DIAC*	Unexplained chronic diarrhoea (> 1month for adults; >14 days for children)	3	3	0	0	1	1
DIAS	Diarrhoea (duration <1 month - adults; <14 days - children)	88	88	1	1	0	0
ENC*	HIV encephalopathy	4	4	1	1	1	1
FBLS	Focal brain lesion	88	88	1	1	0	0
FEVC*	Unexplained persistent fever (> 1 month)	3	3	0	0	1	1
FNID*	Fungal nail infections (fingers or toes)	88	2	0	1	0	1
FNIF*	Fungal nail infections of fingers	2	88	1	0	1	0
HERP	Herpes simplex virus ulcers (duration > 1 month)	4	4	0	0	1	1
HERPS*	Herpes simplex virus ulcers	88	88	1	1	0	0
HERPV*	Visceral herpes simplex infection	4	4	1	1	1	1
HG	Hodgkins Lymphoma	88	88	1	1	0	0
HIST	Histoplasmosis extrapulm.	4	4	1	1	1	1
HPVE*	Extensive human papilloma virus infection	88	2	1	1	0	1
HSM*	Hepatosplenomegaly	88	2	0	0	0	1
HZM*	Herpes zoster (more than one dermatome)	88	88	1	1	0	0
HZS*	Herpes zoster (single dermatome)	2	2	1	1	1	1
ISDI	Isosporiasis diarrhoea (duration > 1 month)	4	4	0	0	1	1
ISDS*	Isosporiasis diarrhoea	88	88	1	1	0	0
KS	Kaposi Sarcoma	4	4	1	1	1	1
LEIS	Leishmaniasis visceral	4	88	1	1	1	0
LEU	Progressive multifocal leucoencephalopathy	4	4	1	1	1	1
LGE*	Lineal gingival erythema	88	2	1	1	0	1
LIP*	Lymphoid interstitial pneumonitis	88	3	0	1	0	1
MC	Mycobacterium avium complex (MAC) or Kanasii extrapulm.	4	4	1	1	1	1
MCDI	Microsporidosis diarrhoea (duration > 1 month)	4	4	0	0	1	1
MCDS*	Microsporidosis diarrhoea	88	88	1	1	0	0

MCI*	Mycobacterium Immune reconstitution syndrome	88	88	1	1	0	0
MCP	Mycobacterium tuberculosis pulmonary	3	3	1	1	1	1
MCPO	Mycobacterium pulmonary other (excluding BCG in children)	88	88	1	1	0	0
MCX	Mycobacterium tuberculosis extrapulmonary	4	4	1	1	1	1
MCXO	Mycobacterium extrapulm. other (excluding BCG in children)	4	4	1	1	1	1
MNUM*	Moderate unexplained malnutrition (60-80% EWFA)	88	3	0	1	0	1
MNUS*	Unexplained severe wasting or malnutrition (<60% EWFA)	88	4	0	1	0	1
MOLC*	Extensive molluscum contagiosum	88	2	1	1	0	1
MYCD*	Any disseminated mycosis	4	4	1	1	1	1
NHG	Non-Hodgkin Lymphoma, not specified	88	88	1	1	0	0
NHGB	Non-Hodgkin Lymphoma, Burkitt (classical or atypical)	88	88	1	1	0	0
NHGI	Non-Hodgkin Lymphoma, diffuse large B-cell lymphoma (immunoblasti or centroblastic)	4	4	1	1	1	1
NHGP	Non-Hodgkin Lymphoma primary brain lymphoma	4	4	1	1	1	1
NHGU	Non-Hodgkin Lymphoma unknown/other histology	88	88	1	1	0	0
NPO*	HIV-associated nephropathy	88	4	1	1	0	1
NUS*	Acute necrotising ulcerative stomatitis, gingivitis or periodontitis	3	3	1	1	1	1
OHLP*	Oral hairy leukoplakia	3	3	1	1	1	1
ORUL*	Recurrent oral ulcerations	2	2	0	0	1	1
PARE*	Parotid enlargement	88	2	1	1	0	1
PCP	Pneumocystis carinii pneumonia	4	4	1	1	1	1
PGL*	Persistent Generalized Lymphadenopathy	1	1	0	0	1	1
PPE*	Papular pruritic eruptions	2	2	1	1	1	1
RTIL*	Lower respiratory tract infection (other than presumed pneumonia) ?	88	88	1	1	0	0
RTIR*	Recurrent or chronic respiratory tract infection (RTIs, sinusitis, bronchitis, otitis media, otorrhea, pharyngitis)	2	2	0	0	1	1
RTIU*	Upper respiratory tract infection	88	88	1	1	0	0
RVF*	Acquired HIV-associated recto-vaginal fistula	88	4	1	1	0	1
SAME	Salmonella bacteraemia (non-typhoid) (single episode)	88	88	1	1	0	0
SAM	Salmonella bacteraemia (non-typhoid) recurrent	4	88	0	0	1	0
SEBD*	Seborrheic dermatitis	2	2	1	1	1	1
TOX	Toxoplasmosis brain (outside neonatal period)	4	4	1	1	1	1
WAST	HIV Wasting Syndrome	4	88	1	0	1	0
WTLM*	Moderate unexplained weight loss (<10% of body weight)	2	88	1	0	1	0
WTLS*	Severe unexplained weight loss (>10% of body weight)	3	88	1	0	1	0

List 4 - Codes for last contact (LAST_CONTACT_T)
Code source: IeDEA SA codes
Table name: LU :PAT :LAST_CONTACT_T

Codes	Last contact type
1	Visit in the facility
2	Phone call
3	Home visit
4	Hospitalisation
5	Drug pick-up only
6	Visit in another facility
7	Laboratory test received
90	Other
95	Not ascertained
99	Unknown despite attempting ascertainment

List 5 - Codes for outcome (OUTCOME)
Code source: IeDEA SA codes
Table name: LU :PAT :OUTCOME

Codes	Mode of infection
10	Death (HIV-related)
11	Death (HIV relationship unknown)
12	Death (not HIV-related)
20	Alive and in care at your facility
21	Known to be alive and in care at another facility
22	Known to be alive and patient is not in care
23	Known to be alive but not known whether patient is in care
30	Transfer out within the same service, vital status after transfer out unknown
31	Transfer out to a different service, vital status after transfer out unknown
40	Loss to follow-up despite active tracing attempted
41	Loss to follow-up (not actively traced)
90	Other
95	Not ascertained

List 6 - Codes for cause of death (DEATH_C1 – 3)
*Code source: HICDEP codes; new codes denoted by **
Table name: LU :PAT :DEATH_C

For HIV-related and Aids defining events (8.*), it is expected that the associated event will be recorded in the OI table.

Codes	Cause of Death
1	Myocardial Infarction
2	Stroke
3	Other cardiovascular diseases
4	Symptoms caused by mitochondrial toxicity
4.1	Lactic acidosis
5	Complications due to diabetes mellitus

6	Pancreatitis
7	Complications due to hepatitis
7.1	Hepatitis related
7.2	Liver failure not related to hepatitis or mitochondrial toxicity
8	HIV-related
8.1	AIDS defining event
8.2	Invasive bacterial infection
9	Renal failure
10	Bleeding (haemophilia)
20	Non AIDS defining cancer
88*	Not applicable
90	Other
91	Suicide
92	Drug Overdose
93	Accident
95*	Not ascertained
99	Unknown, Fatal case with no information

List 7 - Codes for primary caregiver (CAREG)
Code source: IeDEA SA codes
Table name: LU :PAT :CAREG

Codes	Primary caregiver
1	Mother
2	Father
3	Grandmother
4	Other family member
5	Institution
6	None
90	Other
88	Not applicable
95	Not ascertained
99	Unknown despite attempting ascertainment

List 8 - Codes for person informed of the HIV status of the child (DISCL_CG)
Code source: IeDEA SA codes
Table name: LU :PAT :DISCL_CG

Codes	Disclosure to caregiver
1	Mother
2	Father
12	Both parents
3	Grandmother
4	Other primary caregiver
90	Other
88	Not applicable
95	Not ascertained
99	Unknown despite attempting ascertainment

2.2 Laboratory data (LAB table)

Table 2 details the laboratory data that should be included in the LAB table. All available data from the date of first visit should be included.

Notes:

- Results of laboratory tests must be provided in the units specified
- Results of laboratory tests can be entered in one of two fields – a numeric field (LAB_V) and a coded text field (LAB_T) (for very high and/or undetectable viral loads, and for TB microscopy and culture results).
- TB microscopy and culture results should only be entered in the coded result field (LAB_T) as follows, and not in the numeric field (LAB_V):
- For viral loads, there is an additional field to indicate the lower limit of detection of the assay used. This field should be entered as not-applicable (Code = -88) for other laboratory results.
- For TB sensitivity results, there are 2 additional fields. The first (TB_DRUG) where the drug to which sensitivity testing has been done is entered, and the second (SENS), where the sensitivity is recorded using the standard yes/no format. These fields should be entered as not-applicable (Code = 88) for other laboratory results.
- Both CD4 percentage and absolute count should be included on paediatric patients until they are 16 years old.
- There is no code for unknown values of for laboratory test results as tests of which the result is unknown should not be included in the dataset.
- Only dates in the DMY format are permissible in this table

Table 2 – Variables to be included in the table LAB

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
LAB_DMY	Date (for example dd/mm/yy)	Date when specimen was taken
LAB_ID	Text (see List 9)	Code representing the measurement
LAB_V	Numeric (for example 44)	Numeric value of measurement Leave blank if result entered as code (LAB_C)
LAB_T	Text Lower than limit of detection for viral loads should be entered as “LDL” TB microscopy and culture results should be entered as follows: - Paucibacillary 1+ 2+ 3+ Unknown +	Text result eg. “> 6 000 000” or “P+++” Leave blank if result entered as number (LAB_V)
RNA_L	Numeric -88 = Not applicable -99 = Unknown	Lower limit of detection of RNA assay (Enter -88 for laboratory tests other than viral load)

TB_DRUG	Text with codes: INH_L = Isoniazid low dose INH_H = Isoniazid high dose INH_U = Isoniazid – dose unspecified PZA = Pyrazinamide RIF = Rifampicin ETN = Ethionamide ETB = Ethambutol STREP = Streptomycin QUI = Quinolone 88 = Not applicable	TB Drug against which sensitivity has been tested. (Enter 88 for laboratory tests other than viral load)
DRUG_RES	Numeric with codes: 0 = No (Sensitive) 1 = Yes (Resistant) 88 = Not applicable	Is Mycobacterium TB cultured **RESISTANT** to drug in TB-DRUG field? (Enter 88 for laboratory tests other than viral load)

List 9: Codes for measurement type (LAB_ID)
*Code source: HICDEP codes; new codes denoted by **
Table name: LU :LAB :LAB_ID

Codes	Measurement
ALB	Albumin (g/L)
ALT	Alanine-Aminotransferase (UI/L)
AST	Aspartate aminotransferase (UI/L)
CD4A*	CD4 absolute cell count (cells/µl)
CD4P*	CD4 percentage (%)
CHOL	Cholesterol (mmol/L)
CRE	Creatinine (µmol/L)
HAEM	Haemoglobin (g/dl)
LACT	Lactate (mmol/L)
LYMP	Total lymphocyte count (cells/µl)
NEUT	Neutrophil count (x1000/mm^3)
PLT	Platelets (cells/µl)
RNA*	HIV-RNA measurement value (copies/ml)
TBC*	TB culture
TBM*	TB microscopy
TBS*	TB sensitivity
TG	Triglycerides (mmol/L)
URE	Urea (mmol/L)
WBC	White cell count (x1000/ mm^3)

2.3 Antiretroviral drug variables (ART table)

Table 3 details the data on antiretroviral treatment that should be included in the ART table. As previously mentioned, preferably we will receive one line per drug, each with its prescription, start and stop date.

Notes:

- All antiretroviral drugs to which a patient has been exposed (including PMTCT exposure of both pregnant women and infants peri- or postnatally) and PEP should be included with either the dates of starting and stopping the individual drugs, **OR** the number of doses **OR** the duration of treatment.
- History of exposure to antiretroviral drugs prior to commencing care at the reporting facility should be reconstructed as far as possible and included in this table, making use of appropriate drug codes for unknown regimens and date/time codes for unknown start and stop dates or unknown durations.

Table 3 – Variables to be included in ART table

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
ART_ID	ATC (for example NVP – see List 10)	Type of antiretroviral drug
ART_SD_DMY	Date(dd-mm-yyyy)	Date of starting each antiretroviral drug (start date). Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
ART_SD_Y	Numeric (e.g. 2003) 8888 = Exact start date entered in appropriate field 9999 = Unknown despite attempting ascertainment 9995 = Not ascertained	Year of starting drug
ART_SD_M	Numeric (e.g. 7) 88 = Exact start date entered in appropriate field 99 = Unknown despite attempting ascertainment 95 = Not ascertained	Month of starting drug
ART_RS	Numeric with codes (See List 11)	Reason for receiving ART
ART_FORM	Numeric with codes 1 = Tablet/capsule 2 = Syrup/Suspension 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Type of formulation

ART_COMB	Numeric with codes 1 = Individual drug 2 = Part of a fixed dose combination 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Is drug part of a fixed dose combination?
ART_ED_DMY	Date(dd-mm-yyyy)	Date of stopping each antiretroviral drug (end date) Enter exact date in this field if known. If unknown leave blank and enter **EITHER** month and year as far as possible in fields below **OR** number of doses **OR** duration in weeks in the appropriate fields.
ART_ED_Y	Numeric (e.g. 2004) 8888 = exact end date or number of doses or duration in weeks entered in appropriate fields 9999 = Unknown despite attempting ascertainment 9995 = Not ascertained	Year of stopping drug
ART_ED_M	Numeric (e.g. 7) 88 = exact end date or number of doses or duration in weeks entered in appropriate fields 99 = Unknown despite attempting ascertainment 95 = Not ascertained	Month of stopping drug
NO_DOSES	Numeric (e.g. 1) 888 = end date or duration in weeks entered in appropriate fields 999 = Unknown despite attempting ascertainment 995 = Not ascertained	Number of doses of drug e.g. 1 for single dose Nevirapine
NO_WEEKS	Numeric (e.g. 12) 888 = end date or number of doses entered in appropriate fields 999 = Unknown despite attempting ascertainment 995 = Not ascertained	Number of weeks of receiving drug e.g. 12 for AZT from 28 weeks of pregnancy delivering at term
ART_END_RS	Numeric with codes (See List 12)	Reason for stopping antiretroviral drug
INFO_SOURCE	Numeric with codes 1 = Clinical records at this facility 2 = Clinical records/letter from another facility 3 = Patient/caregiver report 4 = Likely protocol in use 90 = Other 99 = Unknown	Source of information about ART

List 10: Anti-retroviral drugs : (ART_ID)
Code source: ATC classification: Anatomical Therapeutic Chemical
Table name: LU :ART :ART_ID

ATC codes	Antiretroviral treatment
J05A	Drug unspecified (i.e. single drug, totally unknown)
J05AE	PI unspecified
J05AE01	Saquinavir (gel, not specified)
J05AE01-SQH	Saquinavir hard gel (INVIRASE)
J05AE01-SQS	Saquinavir soft gel (FORTOVASE)
J05AE02	Indinavir (CRIXIVAN)
J05AE03	Ritonavir (NORVIR)
J05AE03-H	Ritonavir high dose (NORVIR)
J05AE03-L	Ritonavir low dose (NORVIR)
J05AE04	Nelfinavir(VIRACEPT)
J05AE05	Amprenavir (141W94) (AGENERASE)
J05AE06	Lopinavir/Ritonavir (ABT-378/r, Kaletra)
J05AE07	Fosamprenavir
J05AE-ATV	Atazanavir (ZRIVADA)
J05AE-GW4	GW433908/VX-275 (Drug phase III) (PROGENERASE)
J05AE-TMC	TMC 114 (Tibotec)
J05AE-TPR	Tipranavir (trial drug)
J05AF	NRTI unspecified
J05AF01	Zidovudine (AZT, RETROVIR)
J05AF02	Didanosine (ddI) (VIDEX)
J05AF03	Zalcitabine (ddC) (HIVID)
J05AF04	Stavudine (d4T) (ZERIT)
J05AF05	Lamivudine (3TC, EPIVIR)
J05AF06	Abacavir (1592U89) (ZIAGEN)
J05AF07	Tenofovir (TDF, VIREAD)
J05AF08	Adefovir (PREVEON)
J05AF09	Emtricitabine (FTC, EMTRIVA)
J05AF10	Entecavir
J05AF30-KIV	Kivexa
J05AF30-TZV	Trizivir
J05AF-FOZ	Fozivudinetidoxi
J05AF-LDN	Lodenosine (trialdrug)
J05AG	NNRTIunspecified
J05AG01	Nevirapine (VIRAMUNE)
J05AG01-SD	Nevirapine (VIRAMUNE) single dose
J05AG02	Delavirdine (U-90152) (RESCRIPTOR)
J05AG03	Efavirenz (DMP-266) (STOCRIN, SUSTIVA)
J05AG-LOV	Loviride
J05AG-TMC	TMC 125 (Tibotec)
J05A-PBT	Participant in Blinded Trial
J05AR*	ART regimen and drug unspecified (i.e. both number and names of drugs totally unknown)
J05AX07	Enfurvirtide (FUZEON, T-20/Ro 29-9800)
L01XX05	Hydroxyurea/Hydroxycarbamid (LITALIR)

List 11: Codes for reason for receiving ART (ART_RS)
Code source: IeDEA SA codes
Table name: LU :ART :ART_RS

Codes	Reason
10	MTCT – antenatal (mother)
11	MTCT – peripartum (mother)
12	MTCT – postpartum (mother)
13	MTCT – timing unknown (mother)
20	MTCT – peripartum (infant)
21	MTCT – postpartum (infant)
22	MTCT – timing unknown (infant)
30	ARV as treatment
40	PEP
95	Not ascertained
99	Unknown despite attempting ascertainment

List 12: Reason for treatment discontinuation (ART_END_RS)
*Code source: HICDEP codes; new codes denoted by **
Table name: LU :ART :ART_END_RS

Codes	Reason for treatment discontinuation	AE	CI	FL	Other
1	Treatment failure (i.e. virological, immunological, and /or clinical			1	
1.1	Virological failure			1	
1.2	Partial virological failure			1	
1.3	Immunological failure – CD4 drop			1	
1.4	Clinical progression			1	
10	Hyperlactataemie/lactic acidosis	1			
2	Abnormal fat redistribution	1			
3	Concern of cardiovascular disease	1			
3.1	Dyslipidaemia	1			
3.2	Cardiovascular disease	1			
4	Hypersensitivity reaction	1			
5	Toxicity, predominantly from abdomen/G-I tract	1			
5.1	Toxicity – GI tract	1			
5.2	Toxicity – Liver	1			
5.3	Toxicity – Pancreas	1			
6	Toxicity, predominantly from nervous system	1			
6.1	peripheral neuropathy	1			
7	Toxicity, predominantly from kidneys	1			
8	Toxicity, predominantly from endocrine system	1			
8.1	Diabetes	1			
88	Death (note overlap with N/A in other lists)				1
9	Haematological toxicity (anemia …etc.)	1			
90	Side effects – any of the above but unspecified	1			
90.1	Comorbidity		1		
91	Toxicity, not mentioned above	1			
92	Availability of more effective treatment (not specifically failure or side effect related)				1
92.1	Simplified treatment available				1

92.2	Treatment too complex				1
92.3	Drug interaction		1		
92.4	Drug interaction - commencing TB treatment		1		
92.5	Drug interaction ended - stopping TB treatment				1
93	Structured Treatment Interruption (STI)				1
93.1	Structured Treatment Interruption (STI) – at high CD4				1
94	Patient's wish/ decision, not specified above				1
94.1	Non-compliance				1
95	Physician's decision, not specified above (note overlap with standard code				1
95.1*	Contra-indication expired				1
96	Pregnancy		1		
96.1*	MTCT regimen completed				1
96.2*	Pregnancy ended				1
97	Study treatment				1
98	Other causes, not specified above				1
99	Unknown despite attempting ascertainment				1
99.5	Not ascertained				1

2.4 Opportunistic events (OI table)

Table 4 below details the data on opportunistic events or HIV associated conditions diagnosed during follow up that should be included in table OI.

History of opportunistic events prior to commencing care at the reporting facility should be reconstructed as far as possible and included in this table, making use of appropriate date/time codes for unknown start and end dates. It is anticipated that the end date of OIs will frequently be unknown.

Table 4 – Variables to be included in OI table

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
OI_ID	Text (for example PCP - see List 3 – Disease codes – under PAT table)	Type of opportunistic event
OI_SD_DMY	Date(dd-mm-yyyy)	Date of start of each opportunistic event. Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
OI_SD_Y	Numeric (e.g. 2001) 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of start of event
OI_SD_M	Numeric (e.g. 11) 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of start of event

OI_ED_DMY	Date(dd-mm-yyyy)	Date of end of each opportunistic event. Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below If OI is ongoing (has not yet ended) leave blank and enter appropriate code in field below
OI_ED_Y	Numeric (e.g. 2001) 8885 = Ongoing 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of end of event
OI_ED_M	Numeric (e.g. 11) 85 = Ongoing 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of end of event
DIAG_METH	Numeric (see List 13)	Method of diagnosis

List 13: Diagnosis Method of Opportunistic Event (DIAG_METH)
Code source: IeDEA SA codes
Table name: LU :OI :DIAG_METH

Codes	Diagnosis Method
10	clinical only
11	clinical & radiology
12	clinical and endoscopy
20	microscopy for infectious agent
21	culture of infectious agent
30	blood antibody test
31	site specimen (non-blood) antibody test
40	tissue histology
90	other
95	Not ascertained
99	Unknown despite attempting ascertainment

2.5 Follow-up clinic visits (VIS table)

Table 5 below details the information to be included in the **VIS table**. Please include all visits for each patient since the first visit at the reporting facility, and where possible visits at previous facilities. Weight, height and head circumference left blank will be assumed to have not been ascertained.

Table 5 – Variables to be included in VIS table

Name	Format and definitions	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
VISIT_DMY	Date (for example dd/mm/yy)	Date of visit patient
VISIT_FAC	Numeric with codes 1 = Visit at this cohort's facility 2 = Visit at another facility 99 = Site of visit unknown	Facility at which visit took place
WEIGHT	Numeric (for example 75)	Weight in kilos (kg)
HEIGHT	Numeric (for example 75)	Height in centimeters (cm)
CTX	Numeric with codes : 1 = yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Cotrimoxazole status
INH	Numeric with codes : 1 = Yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Isoniazid status
FLU	Numeric with codes : 1 = Yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Fluconazole status
HEADC	Numeric (for example 75)	Head circumference in centimeters (cm)
SCHOOL_Y	Numeric with codes 0 = No school 1 = At school 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Schooling for children >5 years. For adults and children less than 5 years, enter 88.

3 Variables to be included in additional tables

3.1 Family and partner linkages (LINK table)

Table 6 details the information on family members (partners, children and siblings) that should be included in the LINK table.

All family members receiving HIV care should be listed. This includes those receiving care within the reporting cohort as well as those receiving care at other sites.

The cohort-specific identifiers of family members receiving HIV care at the reporting site should be included.

Table 6 – Variables to be included in the table LINK

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
LINK_REL	Numeric with codes (See List 14)	Relationship of family member to patient
LINK_COHORT	Text with codes (See List 15)	Cohort within which family member is receiving HIV care
LINK_ID	Free (numerical or alphanumerical) -88 = Not applicable -95 = Not ascertained -99 = Unknown despite attempting ascertainment	Unique patient identifier of family member Enter -88 if family member in care at non-IeDEA site.

List 14 - Codes for relationship of family member to patient (LINK_REL)
Code source: IeDEA SA codes
Table name: LU :LINK :LINK_REL

Codes	Relationship
1	Mother
2	Father
3	Child
4	Sibling
5	Spouse/partner
90	Other
95	Not ascertained
99	Unknown despite attempting ascertainment

List 15 - Cohort where family member is receiving care (LINK_COHORT)
Code source: To be created by transferring site
Table name: LU :LINK :LINK_COHORT

Codes	Cohort
Cohort ID	Cohort description

3.2 Pregnancy information (PREGNANCY table)

Table 7 details information to be included in the PREGNANCY table. This table contains information on all pregnancies since the patient was known to be HIV-infected, including spontaneous abortions/ miscarriages and terminated pregnancies, and their outcomes.

Table 7 – Variables to be included in PREGNANCY table

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier for patient
PREG_DIAG_DMY	Date (dd-mm-yyyy)	Exact date when patient first presents as pregnant
PREG_DUR_DIAG	Numeric (e.g. 12) 99 = Unknown	Estimated duration of pregnancy in weeks when patient first presents as pregnant
PREG_END_DMY	Date (dd-mm-yyyy)	Exact date of delivery, spontaneous abortion or termination Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
PREG_END_Y	Numeric (e.g. 2003) 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of delivery, spontaneous abortion or termination
PREG_END_M	Numeric (e.g. 9) 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of delivery, spontaneous abortion or termination
PREG_ED	Numeric (e.g. 36) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Estimated duration of entire pregnancy in weeks
PREG_OUTCOME	Numeric with codes 1 = Live birth 2 = Still birth 3 = Termination of pregnancy 4= Spontaneous abortion (miscarriage) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Outcome of pregnancy
INF_WT	Numeric (e.g. 2.9) 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Weight of delivered infant. If spontaneous abortion or termination, enter 88

NEONATAL_DEATH	Numeric with codes 0 = No 1 = Yes 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Did delivered live infant die within 1 month of birth? If stillbirth, spontaneous abortion or termination, enter 88
BIRTH DEFECT_Y	Numeric with codes 0 = No 1 = Yes 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Did fœtus or infant have any congenital malformations?
BIRTH_DEFECT_TYPE	Text	Free text description of malformations

3.3 Parental Health (PAR_HEALTH table)

Table 8 details variables to be included in the table PAR_HEALTH. This table contains information on parental health status.

This table is linked to the visit table, so ideally there is an update on parental health status at every visit. Alternatively, this table should be filled in at least once, either for the first visit at your facility or the date of start of HAART.

For patients over 16 years of age, no entries are required into this table (i.e. this table is not required at all for sites that have only patients over 16 years of age in their care).

While information on parental health is very valuable, it is acknowledged that many sites do not collect this information. If only information at the child's first visit or at the start of HAART is collected, this should be included with the appropriate visit date. If no information on parental health is collected, this table can be omitted.

Table 8: Variables to be included in the PAR_HEALTH table

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier for patient
VIS_DMY	Date (dd/mm/yy)	Date of parental health evaluation (probably same as clinic visit date)
MAT_DEATH	Numeric with codes 0 = No (Alive) 1 = Yes (Dead) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Maternal status: Mother deceased?

MAT_HIV	Numeric with codes 0 = Negative 1 = Positive 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Mother's HIV status if available
MAT_TTT	Numeric with codes 0 = No treatment 1 = CMX only 2 = HAART only 12 = CMX and HAART 88 = Not applicable (mother HIV negative or deceased) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Mother's treatment if available
PAT_DEATH	Numeric with codes 0 = No (Alive) 1 = Yes (Dead) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Paternal status: Father deceased?
PAT_HIV	Numeric with codes 0 = Negative 1 = Positive 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Father's HIV status if available
PAT_TTT	Numeric with codes 0 = No treatment 1 = CMX only 2 = HAART only 12 = CMX and HAART 88 = Not applicable (father HIV negative or deceased) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Father's treatment if available

3.4 Tuberculosis information (TB table)

This table is for capturing details of the TB episodes during HIV follow-up. Tests related to TB can be included in the LAB table. Where possible this data can be derived from the electronic TB register.

Table 9 – Variables to be included in the table TB

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
REG_DMY	Date (dd/mm/yy)	Date registered with TB
REGID	Text (eg. 2272007) -95 = Not ascertained -99 = Unknown despite attempting ascertainment	TB register number
RAD	Numeric with codes 0 – Not done 1 – Normal 20 – Abnormal unspecified 21 – Abnormal - not consistent with current TB 22 – Abnormal - consistent with current TB unspecified 23 – Abnormal – consistent with current TB – Cavity on right 24 - Abnormal – consistent with current TB – Cavity on left 25 - Abnormal – consistent with current TB – Bilateral cavities 26 - Abnormal – consistent with current TB - No cavities 99 = Unknown despite attempting ascertainment	Radiography findings if done
RESISTANT	Numeric with codes 0 – No 1 – MDR 2 – XDR 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Resistance data based on sensitivities Note: Exact results of sensitivities should be record in the LAB table. Code as MDR if … to more than one drug and XDR if… Categories MDR and XDR should be for the worst resistance status during the episode.
TB_START_DMY	Date (dd/mm/yy)	Date starting TB treatment
TB_END_DMY	Date (dd/mm/yy)	Date ending TB treatment or date of outcome
CAT	Numeric with codes 1 – Newly diagnosed for the first time 2 – After relapse 3 – After default 4 – After failure 95 = Not ascertained 99 = Unknown despite attempting ascertainment	TB Category
CLASS	Numeric with codes 1 - Pulmonary 2 – Extra-pulmonary 3 – Both pulmonary and extra-pulmonary 4 - Primary 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Classification of episode

SITE	Numeric with codes 1 – Bones/Joints (A18.0) 2 – Lymph nodes (A16.3) 3 – Meningitis (A17.0) 4 – Miliary (A19.9) 5 – Pleura (A16.5) 9 – Other sites (A18.8) 88 – Not applicable as pulmonary or primary only 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Site of disease if extra-pulmonary component diagnosed
REGIMEN	Numeric with codes 1 – 2HRZE 4HR - Regimen 1 2 –2HRZES 1HRZE 5HRE - Regimen 2 3 – 2HRZ 4HR - Regimen 3 4 –Other Regimen 95 = Not ascertained 99 = Unknown despite attempting ascertainment	TB treatment regimen
REG_OTHER	Text	Text field for other regimen not included in codes for REGIMEN field above
TB_OUTCOME	Numeric with codes 1 – Completed 2 – Cured 3 – Failed 4 – Interrupted 5 – Defaulted 6 – Treatment ongoing 7 - Died 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Outcome of TB episode

3.5 Trial/research study enrolment information (TRIAL table)

Table 10 details the data that should be included in the TRIAL table. This table is only for sites running trials or research studies. Any trial/research study (apart from cohort analysis of routine data) on which a patient has been enrolled should be entered together with the dates of entering and leaving each trial. Sites should send an additional coding table of the trials running at their site.

Table 10 – Variables to be included in the table TRIAL

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
TRIAL_START_DMY	Date (for example dd/mm/yy)	Date of enrolment onto trial
TRIAL_END_DMY	Date (for example dd/mm/yy)	Date of completion/ disenrolment Leave blank if patient is still enrolled on trial
TRIAL_ID	Free (numeric or text) codes (See List 16)	Name of trial on which patient is enrolled Each site to send their own List with coding and description of trial

List 16: Example of codes for trial name (TRIAL_ID)
Code source: Site to supply own codes
Table name: LU :TRIAL :TRIAL_ID

Codes (Text or Numeric)	Trial name (text field)	Short description of trial (Memo field)
INH	INH trial	Trial of thrice weekly vs daily INH prophylaxis in HIV-infected children
TB	TB treatment duration trial	Trial of 6 month vs 9 month chemotherapy in HIV-infected children

4 Meta-data

This table contains information about the data transfer itself.

Table 11 – Variables to be included in the table META

Name	Format	Description
COHORT	Text	Name of the cohort
ENROLS_DMY	Date (for example dd/mm/yy)	Date of start of enrolment
ENROLE_DMY	Date (for example dd/mm/yy)	Date of end of enrolment
FU_CLOSE_DMY	Date (for example dd/mm/yy)	Date of last possible follow-up
ASC_DMY	Date (for example dd/mm/yy)	Date of last possible outcome ascertainment
LTF_DEF	Numeric	For patients classified by the site as LTF, the number of days used to define LTF
REPORTER	Text	Name of person responsible for data transfer
TRANSFER_DMY	Date (for example dd/mm/yy)	Date extracted
EMAIL	Text	Email address of site person responsible