Outcomes of infants starting Antiretroviral Therapy in Southern Africa

by

Mireille Porter
MLNMIR001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In partial fulfillment of the requirements for the degree

MASTER OF PUBLIC HEALTH

In the School of Public Health and Family Medicine, Faculty of Health Sciences,
University of Cape Town

June 2014

Supervisors:

Dr. Mary-Ann Davies

School of Public Health and Family Medicine, University of Cape Town

Associate Professor Brian Eley

School of Child and Adolescent Health, University of Cape Town

PREAMBLE

Declaration

I, Mireille Porter (Student number MLNMIR001) hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: ……

Date: …….

For Nkosinathi

Abstract

Title: Outcomes of infants starting Antiretroviral Therapy (ART) in Southern Africa.

Background and Rationale: Within the global burden of the Human Immune Deficiency Virus (HIV) stands a distinct group – HIV infected infants. They are a physically, physiologically, developmentally and socially vulnerable group who differ considerably from their adult and child HIV infected counterparts. Distinguished in part by their multiple age-specific complexities in testing, treatment and monitoring these infants ultimately experience accelerated disease progression and an increased risk of morbidity and mortality. Advances in evidence gained from trials of the benefits of early initiation of ART in infants have resulted in international treatment guidelines changes and an increase in velocity and coverage of infant ART provision. However, there is limited published data on the outcomes of infants starting ART in routine care in Southern Africa.

Objectives: To describe the baseline characteristics of infants starting first line ART in routine care setting in Southern Africa. To describe and examine the outcomes of these infants including clinical, immunological and virological responses and to identify the determinants for these outcomes.

Method: A retrospective analysis was performed of prospectively collected cohort data of infants that initiated ART in routine care settings at the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) collaborative sites. A description of demographic, clinical, laboratory and program baseline characteristics is provided and longitudinal profiles of response variables are described. The Kaplan-Meier method was used to assess time to outcomes of

mortality and virological outcome. Cox Proportional Hazards models identified those baseline characteristics associated with each of these outcomes. Competing Risk Analysis provides Cumulative Incidence Functions for mortality and programmatic outcomes. Multiple imputation was conducted and Rubin's Rules provided pooled estimates from Survival Analysis.

Part A: The study protocol as submitted for Departmental and Ethical Approval is presented here. It includes the background, rationale and methodology of the research done for this mini-dissertation.

Part B: A structured literature review is presented of articles pertaining to observational research conducted in Sub-Saharan Africa on the outcomes of infants initiating antiretroviral therapy.

Part C: Here a journal-ready manuscript according to the requirements of the Pediatric Infectious Disease Journal (author's information included as **Appendix F)** is presented.

Appendices: Includes all additional documentation necessary as addendums in the presentation of the above parts of the mini-dissertation.

Results: 4945 infants initiated ART at a median (IQR) age of 5.9 months (3.7-8.7) and were followed for a median (IQR) of 11.2 months (2.8-20.0). At initiation of ART 77% of infants were classified as World Health Organisation (WHO) clinical stage 3 or 4 and 87% met the 2006 WHO definition of severe immunosuppression. 3-year mortality probability was over 15% and Loss to Follow-up (LTFU) 29%. Severe immune suppression (adjusted Hazard ratio (aHR) 2.19, 95%CI 1.44-3.33), WHO stage 3/4 (aHR 1.36, 95% CI 1.04-1.78), lower weight-for-age z-score (WAZ

<-3 compared to >-2 aHR 2.34, 95%CI 1.78-2.80) and initiation of ART in 2010 or after (aHR 0.75, 95%CI 0.59-0.94) were each found to be independently associated with mortality. The proportion of infants attaining virological suppression by 12 months was 56.1% (95% Confidence Interval (CI) 53.2-59.1). A viral load of 1 million copies/ml or above was found to be associated with a longer time to virological suppression (aHR 0.78, 95% CI 0.68-0.89).

Conclusion: Amongst infants initiating ART in Southern Africa between 2004 and 2012 there was a predominance of severe baseline disease severity. Infant immunological and virological responses were suboptimal and high levels of loss to follow up and mortality were seen.

The Vancouver referencing style has been used for Part A and B of this mini-dissertation however, in keeping with the instructions for authors as stipulated by the Pediatric Infectious Disease Journal, Part C: the Journal Ready Manuscript includes references in the style of the United Stated National Library of Medicine.

Acknowledgements

Thank you to my supervisor Mary-Ann Davies for providing the vision and topic for this mini-dissertation as well as continuous encouragement, review and feedback over the process of completion of this project. Thank you also to my Co-Supervisor, Dr. Brian Eley, for all your assistance with reviewing the many stages of this project and assisting in the reviewing of this final dissertation.

Thank you to Muntanga Mapani, Helena Rabie, Sam Phiri, James Nuttall, Harry Moultrie, Karl Technau, Kathryn Stinson, Robin Wood, Maureen Wellington, Andreas Haas, Janet Giddy and Portia Mutevedzi. Thank you for your role as site investigators in the contribution of data to the IeDEA-SA database. Thank you for your advice and assistance in the review process for the article produced for publication purposes.

Thank you to the staff at the Cape Town IeDEA-SA office: Morna Cornell, Leigh Johnson, Nicola Maxwell and special thanks to Michael Schomaker for his statistical support. I would also like to thank the IeDEA-SA Bern office with special thanks to Fritz Kaeser, Claire Graber and Kelly Goodwin for their roles in data management and project management respectively.

Finally I thank every child who has contributed data to this research, their caregivers, health care providers at participating sites as well as all staff involved in the preparation of data contributed to the IeDEA-SA Southern African Collaboration.

Funding and Conflicts of interest: This study was supported by the National Institute of Allergy and Infectious Disease and the Eunice Kennedy Shriver Institute of Child Health and Human Development (grant 2U01AI069924). The funders did

not participate in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript. The author has no other funding or conflicts of interest to disclose.

Table of Contents

Part 0: Preamble

Declaration 1

Dedication 2

Abstract 3

Acknowledgements 6

List of Tables 14

List of Figures 16

List of Abbreviations 17

Part A: Protocol

Introduction 3

Background 3

Problem Statement and Research Question 6

Rationale for proposed study 7

Study Objectives 8

Methodology 9

Study design 9

Population and sampling 9

Characteristics of study population 9

Inclusion and Exclusion Criteria 9

Exclusion criteria for infants 10

Sampling 10

Measurement 11
Research Procedures and Data Collection Methods 11
Variables for inclusion 11
Validity and reliability of measuring instruments 13
Potential Bias and Confounding 14
Data Analysis 16
Ethical Considerations 18
Ethical Approval 18
Risk classification 18
Potential risks and discomforts 18
Potential Benefits 18
Consent, Privacy and Confidentiality 19
Involvement of vulnerable persons 19
Stakeholders 20
Dissemination of Results 20
Logistics 20
Timetable 20
Budget 22
Contact Details 22
References 22

Part B: Literature Review

Introduction 4

Background 4

Aim and Objectives 5

Review Process 7

Structure of the Review 7

Search Strategy 7

Inclusion Criteria 8

Exclusion criteria 8

Articles Published 9

Quality and Comparability of Studies 10

Primary aims and focus of the study 10

Study Designs 11

Infant subgroup definition 11

Sample Size 11

Follow Up 11

Study Population and Inclusion Criteria 12

Infant initiation guidelines 13

Confounders 14

Missing Data 15

Results 22

Baseline Characteristics 22

Age 22

Virological 23

Immunological 23

Clinical disease 24
Growth 25
PMTCT exposure 26
Cotrimoxazole Prophylaxis 27
Tuberculosis 28
Regimen 28
Initiation delay 29
Other Baseline Characteristics 29
Outcomes 34
Mortality 34
Virological Outcomes 36
Immunological Outcomes 37
Clinical Outcomes 38
Growth Measures 38
Loss to Follow Up 39
Loss to Program 41
Other 42
Determinants of infant outcomes 47
Summary, Interpretation and needs for further research 50
References 57

Part C: Journal Ready Manuscript

Title Page 1

Abstract 2

Introduction 4

Methods 6

Study design and population 6

Key cohort characteristics and outcomes 7

Statistical methods 8

Results 10

Cohort Characteristics 10

Baseline Characteristics 10

Mortality and programmatic outcomes 13

Baseline Characteristics associated with mortality 14

Response on ART for infants remaining in care >12 months 16

Anthropometric Response 16

Immunological Response 17

Haemoglobin 17

Virological response 18

Discussion 19

Conclusion 23

Acknowledgments 24

References 25

Figure Legend 31

Appendices

Appendix A: The International Epidemiologic Databases to evaluate AIDS in Southern Africa (IeDEA-SA) Data Transfer Protocol 1

Appendix B: IeDEA –SA Concept Sheet for Proposed Analysis 57

Appendix C: Official letter of ethical approval from University of Cape Town (UCT) Faculty of Health Sciences Research Ethics Committee 65

Appendix D: Official letter of ethical approval from UCT Faculty of Health Sciences Research Ethics Committee for parent project by IeDEA. 67

Appendix E: Annual Progress Report/Renewal by Human Research Ethics Committee for parent protocol 68

Appendix F: Instructions for Authors: The Pediatric Infectious Disease Journal (PIDJ) 69

Appendix G: Supplementary tables for journal ready manuscript 86

List of Tables

Part A: Protocol

Table 1. Variables of infant and program characteristics at initiation of ART 12

Table 2. Variables of Primary Outcomes 13

Table 3. Variables of Longitudinal Response Variables 13

Table 4. Timetable for completion of mini-dissertation 21

Part B: Literature Review

Table 1a. Quality and Comparability - Analytic Studies 16

Table 1b. Quality and Comparability - Descriptive Studies 17

Table 2a. Infant subgroup measurements and Validity – Analytic 19

Table 2b. Infant subgroup Measurements and Validity – Descriptive 20

Table 3a. Baseline Characteristics – Analytic 31

Table 3b. Baseline Characteristics – Descriptive 32

Table 4. Loss to Program Outcomes 42

Table 5a. Outcomes described – Analytic Infant Outcomes 44

Table 5b. Outcomes described- Descriptive infant outcomes 45

Table 6. Determinants of infant outcomes 49

Part C: Journal Manuscript

Table 1. Baseline Characteristics of infants initiating ART, 2004-2012 11

Table 2. Survival Analysis: Cox regression for predictors of mortality 15

Table 3. Figure legend..... 31

Appendices

Supplementary Table 1: Estimates from Complete Case Survival Analysis for the outcome of mortality 86

Supplementary Table 2: Estimates from Survival Analysis (including imputed data and complete case analysis) for the outcomes of mortality in a subset of infants from South African sites including analysis of the associations of baseline viral load category therewith 87

Supplementary Table 3: Estimates from Survival Analysis (including imputed data and complete case analysis) for the outcomes of virological suppression in infants from South African sites with a minimum of a baseline and one other virological measure 88

List of Figures

Part B: Literature Review

Figure 1: Flow chart showing the identification review articles. 9

Part C: Journal Manuscript

Figure 1a. Kaplan-Meier estimates for outcomes of initiating ART in Southern Africa. 14

Figure 1b. Competing Risk Analysis Cumulative Incidence Functions for outcomes of initiating ART in Southern Africa. 14

Figure 1c. Kaplan-Meier estimates for outcome of mortality by time period of initiation 14

Figure 1d. Kaplan-Meier estimates for outcome of loss to follow-up by time period of initiation 14

Figure 2. Growth response on ART over time for infants remaining in care for at least 1 year. 16

Figure 3a. Changes in median CD4 percent over time on ART for infants remaining in care for a minimum of 12 months. 18

Figure 3b. Changes in median CD4 percent over time on ART for infants remaining in care for a minimum of 12 months. 18

Figure 3c. Changes in median Haemoglobin over time on ART for infants remaining in care for a minimum of 12 months. 18

Figure 3d. Kaplan-Meier estimates of time to virological suppression over time on ART. 18

List of Abbreviations

3TC	Lamivudine
ABC	Abacavir
AZT	Zidovudine
aHR	Adjusted Hazard Ratio
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BAZ	Body Metabolic Index for Age Z -score
BCG	Bacillus Calmette-Guerin
CD4	T cell cluster of differentiation 4
CHER	Children with HIV Early Antiretroviral Therapy Trial
CI	Confidence Interval
D4T	Stavudine
DAIDS	Division of AIDS
DNDi	Drugs for Neglected Diseases Initiative
DTP	Data Transfer Protocol
EID	Early Infant Diagnosis
GIT	Gastrointestinal System
HAART	Highly Active Antiretroviral Treatment
HAZ	Height-for-age Z score
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
IeDEA	International Epidemiologic Database to Evaluate AIDS
IeDEA-	International Epidemiologic Database to Evaluate AIDS in Southern

SA	Africa
INH	Isoniazid Prophylaxis
IRIS	Immune reconstitution Inflammatory Syndrome
IQR	Interquartile Range
LTFU	Loss to Follow-Up
MTCT	Mother to Child Transmission
NHLS	National Health Laboratory Service (South Africa)
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OASIS	Observational Antiretroviral Studies in South Africa
PCR	Polymerase Chain Reaction Test for HIV
PI	Protease Inhibitor
PMTCT	Prevention of Mother to Child Transmission
RNA	Ribonucleic acid
SQL	Structured Query Language
TB	Tuberculosis
TFO	Transfer Out
UNICEF	United Nations Children's Fund
UNAIDS	Joint United Nations Programme on HIV/AIDS
URTI	Upper Respiratory Tract Infection
USA	United States of America
WAZ	Weight-for-age Z-score
WFHZ	Weight-for-height Z-score
WHO	World Health Organisation

VI	Variable Importance
VL	Viral Load
VS	Virological Suppression

PART A: PROTOCOL

Table of Contents

Introduction 3

Background 3

Problem Statement and Research Question 6

Rationale for proposed study 7

Study Objectives 8

Methodology 9

Study design 9

Population and sampling 9

Characteristics of study population 9

Inclusion and Exclusion Criteria 9

Exclusion criteria for infants 10

Sampling 10

Measurement 11

Research Procedures and Data Collection Methods 11

Variables for inclusion 11

Validity and reliability of measuring instruments 13

Potential Bias and Confounding 14

Data Analysis 16

Ethical Considerations 18

Ethical Approval 18

Risk classification 18

Potential risks and discomforts 18

Potential Benefits 18

Consent, Privacy and Confidentiality 19

Involvement of vulnerable persons 19

Stakeholders 20

Dissemination of Results 20

Logistics 20

Timetable 20

Budget 22

Contact Details 22

References 24

List of tables

Table 1. Variables of infant and program characteristics at initiation of ART 12

Table 2. Variables of Primary Outcomes 13

Table 3. Variables of Longitudinal Response Variables 13

Table 4. Timetable for completion of mini-dissertation 21

Introduction

Background

Epidemiology of Infant HIV

Of the 34 million people worldwide estimated to be living with Human Immune Deficiency Virus (HIV), 90% are living in Sub-Saharan Arica and 10% are children less than 15 years of age (1, 2). Despite advances in Prevention of Mother to Child Transmission (PMTCT) programs, including possible reduction of infection to as low as 1% (7) and a global coverage of 56% (8), over 900 infants are infected with HIV every day (9). HIV infected infants form a distinct group whose risks and management needs distinguish them from their adult and child counterparts (1-3). Within this period of rapid physical growth (especially of their developing brain), establishment of a functioning immune system and a rapidly changing physiology, these infants are severely vulnerable to the multiple insults of HIV and its complications (10). The natural history of the disease itself differs significantly in infancy where there is a far more rapid progression to severe disease stages and death (4). Untreated HIV infection in infancy is associated with serious morbidity from opportunistic infections and associated organ damage including HIV encephalopathy and its adverse permanent neurodevelopmental effects (11).

In Southern Africa HIV related illnesses account for between 10 and 28% of under-5 mortality (1, 9, 12). Furthermore in low and middle income countries, such as within this region, without antiretroviral therapy (ART) this infant group has up to a 30% risk of death in their first year of life and 50% by the age of two years (13). This increased risk and vulnerability of the infant subgroup occurs within an environment

that is complicated by concerns relating to PMTCT ART exposure and the provision, administration and monitoring of ART. Additionally these factors interact in an age group known for their unpredictable, variable and rapidly changing physiology (3, 4, 14-18).

Support from Literature

The uniqueness, vulnerability and need for research of infants infected with HIV have been noted by several studies. A 2003 Meta-Analysis of trials in Europe and United States of America (USA) of prognostic markers in HIV Paediatric care highlighted the need to view infants as a distinct group with regards to HIV and its care and management. In this study it was found that when comparing infants to 5 year olds with similar T cell cluster of differentiation 4 (CD4) levels infants had a 6 fold increase in the risk of death (5, 16). Soon followed by several observational studies, this evidence contributed to an emerging understanding of the possible inappropriateness of applying standardised childhood clinical, immunological and virological markers of disease progression to the infant subgroup and in doing so emphasised a need for an improved strategy for treatment initiation (19, 20). In 2004 results from a small open-label phase 1-2 trial by Luzuriaga et al provided evidence of the long term virological benefits of early initiation of infants under 3 months of age (21). In addition to these improved physiological outcomes, early initiation of ART in infants was supported by observational evidence that showed that in keeping with the 2006 World Health Organisation (WHO) immunological criteria for initiation, 85% of HIV positive infants would require ART by 6 months of age (21, 22). The practical and programmatic benefits of early initiation included economic

viability in view of monitoring costs, minimization of loss to follow up and prevention of immunological decline (22).

Amongst this resounding call for definitive evidence and guideline amendment in 2008 a randomised control trial in South Africa - the Children with Human Immune Deficiency Virus Early Antiretroviral Therapy Trial (CHER) reported compelling evidence in support of early treatment of infants (5). This trial quantified the benefits of early initiation of ART before 12 weeks of age compared to deferring ART until WHO 2006 treatment initiation criteria were met and showed a 76% reduction in mortality and 75% reduction in disease progression in the early treatment group. Subsequent substudy analyses have shown specific benefits of early initiation regarding short-term neurodevelopmental outcomes, (23) nutrition and growth (24). These findings resulted in with rapid changes to national and global infant ART guidelines in 2008 calling for all HIV infected infants under the age of 12 months to be commenced on ART regardless of clinical or immunological factors (25). Subsequently 2010 and 2013 guidelines amended this guideline to all children under 2 and under 5 years of age respectively (26, 27).

What further evidence is required?

The CHER trial was successful in quantifying the impact of early initiation of ART in a controlled trial environment with an average age of commencement of ART of 7 weeks, complete availability of appropriate laboratory testing and drug regimens that were all protease inhibitor based, minimisation of loss to follow up and the exclusion of those with comorbid conditions. The possible impact of these highly favourable conditions on the magnitude of the beneficial association of early initiation on infant outcomes leads to a concern about the generalizability of these outcomes to infants

receiving care in routine settings particularly those within resource-scarce regions such as Southern Africa (28). This 'routine-setting' is characterised by concerns of delayed HIV diagnostic and missed testing, poor follow up, non-adherence, limited resources and restricted laboratory access further complicated by the social, diagnostic, monitoring and treatment needs of infants (3, 17, 18, 29, 30). Early initiation cannot occur without early testing and across sub-Saharan Africa only an estimated 28% of HIV exposed infants receive testing prior to 2 months of age, highlighting the need for better access to Polymerase Chain Reaction (PCR) HIV testing and PMTCT linkages (30-33). With HIV-related infant mortality peaking at 2-3 months of age these testing delays, coupled with an average test-to-start interval of 33 days, have the potential to result in poor outcomes (34-36).

In 2010 in light of insufficient treatment options, a paucity of policy and research and a widening gap in coverage rates of ART for children and adults – 28% compared to 56% - (9, 15, 29) the Drugs for Neglected Disease Initiative (DNDi) recognised paediatric HIV as a neglected disease (3).This extremely high risk population, (17, 37) with a severe imbalance between needs and provision of care, not only require evidence based management to save lives but also to "build them a body that lasts a lifetime" as each life saved adds to the evolution of HIV into a chronic disease (10, 38).

Problem Statement and Research Question

Within the context of a severe burden of HIV and the rapid escalation of coverage of ART provision in Southern Africa evidence is needed regarding the routine care practices and outcomes of infants initiating ART. Such evidence is necessary not only to monitor the implementation of guidelines and evaluate their impact but also

to identify predictors of these outcomes in order to inform program development and improvement (39-41). There is however limited data on the outcomes of infants starting ART in routine care in resource scarce settings. Previously published studies, including those discussed here, lack power due to very small sample sizes, an often limited observational period and having been designed for other specific outcomes such as resistance (18, 19, 42-45).

This problem leads to the question: "What are the outcomes of infants starting ART in routine care in Southern Africa?" and "What are the predictors of these outcomes?"

Rationale for proposed study

Funded by the National Institutes of Allergy and Infectious Diseases (NIAID), the International Epidemiology Databases to evaluate AIDS (IeDEA) is an international initiative that pools several large data sets each comprised of HIV infected individuals enrolled in standard care at participating sites (40, 46, 47). With data collected from routine clinical records in a region that is home to over a third of all people living with HIV (1) the IeDEA-Southern Africa (IeDEA-SA) database offers the opportunity to review the extent of implementation of the WHO 2010 guidelines with respect to immediate infant ART initiation and to examine the outcomes and their determinants for infants starting ART in these routine settings. The use of the IeDEA-SA infant ART cohort for this study will thus add to the current limited evidence and knowledge of the outcomes of infants starting ART in routine settings in Southern Africa. Further information including other research objectives of IeDEA-SA can be found on their website at www.iedea-hiv.org.

Study Objectives

The following objectives have been identified for purposes of the study:

1 To describe the baseline characteristics of infants commencing ART in IeDEA sites in Southern Africa. These characteristics include demographic, programmatic and both clinical and chemical markers of HIV disease severity (Virological, Immunological markers where available).

2 To describe and examine the outcomes of infants starting ART in Southern Africa. These outcomes include repeated measures and their change over time as well as final outcomes of death, Loss to Follow Up and Transfer Out.

3 To identify and examine predictors for these outcomes.

Methodology

Study design

This study will be a retrospective analysis of prospectively collected cohort data of infants that initiated ART in routine care settings at the IeDEA-SA collaborative sites. Data for this cohort is collected through routine clinical follow up of these infants within the standard treatment and monitoring of HIV and ART.

Population and sampling

Characteristics of study population

The IeDEA-SA collaboration includes sites from South Africa, Zimbabwe, Mozambique, Malawi, Botswana and Zambia (39). There are approximately 5000 infants who have initiated ART before the age of 12 months amongst 11 participating sites. Data recorded between 2004 and end of 2012 will be included in the analysis.

Inclusion and Exclusion Criteria

IeDEA requires participating sites to be facilities that treat those living with HIV and prospectively collect data in an electronic format (39). Data are captured for all those attending the facility with a documented HIV-1 infection and for whom the date of first visit at the facility is known exactly as per the IeDEA-SA Data Transfer Protocol (DTP) **(Appendix A).**

For purposes of this study sites and participants included in this study are required to meet the following eligibility criteria:

- Sites included require provision of ART for infants (<1 year old) (at least a portion of which initiated ART since 1 January 2010 as this would ensure that each cohort captured a portion of infants initiated after the release of the WHO 2010 guidelines)

- Infants who are HIV infected (recorded PCR diagnosis or presumptive diagnosis) and ART naïve at their first visit (except for PMTCT exposure).

- Infants who initiated a minimum of three antiretroviral drugs on a recorded date before their first birthday.

Exclusion criteria for infants

All infants with missing information on key variables e.g. date of birth, gender and date of initiation will be excluded from the analysis.

Infants identified as being virologically suppressed (HIV-RNA <400 copies/ml) at initiation will be excluded from analysis as this suggests that they may be non-naïve to ART.

Sampling

All infants meeting eligibility criteria will be included in the study therefore no sample size calculation has been done.

Measurement

Research Procedures and Data Collection Methods

Data routinely recorded from participants at every clinic visit are collected on site by site investigators. Data includes baseline and follow up visit data. Data from each site is anonymised and transferred to IeDEA-SA using a Data Transfer Protocol **(Appendix A).** The anonymised data from each of the sites are converted to Structured Query Language (SQL) format, stored, cleaned, merged and analysed (46, 48).

Variables for inclusion

Infant characteristics at baseline initiation of ART

This shall include demographic data of the individual as well as information of PMTCT exposure, anthropometric measures, clinical, immunological and virological markers of disease severity and details of treatment timing and medications. **Table 1.**

Outcomes

The primary outcomes of this study are death, loss to follow up (LTFU) and transfer out (TFO). Dates of these outcomes shall be recorded. **Table 2.** Longitudinal response variables as recorded at subsequent dated follow up visits shall include immunological, virological and growth characteristics of those remaining in care. **Table 3.**

Third Variables

Potential confounders for the different predictor-response relationships such as age and gender will be included in the IeDEA database data extraction process.

Dummy Tables

Table 1: Infant and program characteristics at initiation of ART

Variable	Format	Description
Patient Identifier	Text and numeric	Unique, anonymous, patient identifier
Cohort	Categorical*	Treatment site
Age at initiation of ART	Numerical	Age in months at ART initiation
Gender	Categorical, binary	Male or Female gender
PMTCT exposure	Categorical	Mother or infant exposed to MTCT drugs (peri/post-natally)
Date of first visit at facility	dd-mm-yy	
Date of ART initiation	dd-mm-yy	
First line regimen used	Categorical	Names of each antiretroviral prescribed
Weight	Numerical	Weight in Kilograms (kg)
Height	Numerical	Height in centimetres (cm)
Weight-for-Age	Numerical	Weight for age Z scores (WAZ)
Height-for-Age	Numerical	Height for age Z scores (HAZ)
BMI-for- Age	Numerical	Body Mass index for age Z-score (BAZ)
Weight-for-Height	Numerical	Weight for Height Z scores (WFHZ)
CD4 count	Numerical	CD4 absolute cell count (cells/µl)
CD4 percentage	Numerical	CD4 percentage (%)
Viral load	Numerical	HIV-RNA measurement value (copies/ml)
Haemoglobin	Numerical	Blood Haemoglobin count (g/dl)
WHO Stage	Categorical, ordinal	Clinical WHO stage (I to IV)

Table 2: Primary outcomes

Variable	Format	Description
Outcome	Categorical	Defined as died, lost to follow-up, transferred out
Date of Outcome	dd-mm-yy	Date of event as stated above

Table 3: Longitudinal Response Variables

Variable	Format	Description
Date of each visit	dd-mm-yy	Each date to be recorded with data as below
Height	Numerical	Height in centimetres (cm)
Weight	Numerical	Weight in kilos (kg)
Weight-for-Age	Numerical	Weight for age Z scores (WAZ)
Height-for-Age	Numerical	Height for age Z scores (HAZ)
Body Mass Index for Age	Numerical	Body Mass index for age Z-score (BAZ)
Weight-for-Height	Numerical	Weight for height Z scores (WFHZ)
CD4 count	Numeric al	CD4 absolute cell count (cells/μl)
CD4 percentage	Numerical	CD4 percentage (%)
Viral load	Numerical	HIV-RNA measurement value (copies/ml)
Haemoglobin	Numerical	Blood Haemoglobin count (g/dl)

* Use of categorical variables as per Data Transfer Protocol Lists and coding see **Appendix A** for further details

Validity and reliability of measuring instruments

The validity of data in the IeDEA-SA database is dependent upon the recording of information at the participating sites. The data collated centrally is assessed through a

Data Quality Report and deficiencies in the data are reported to the sites and improvements made where feasible.

Potential Bias and Confounding

Survival Bias

The study of outcomes of HIV positive infants is particularly vulnerable to the effect of Selection Bias through the unintentional selection of a group of "survivors". This Survival Bias arises where death due to HIV occurring prior to initiation of ART naturally precludes inclusion within the observed cohort. Baseline characteristics and outcomes thus will reflect the characteristics of this population of "survivors". This will be addressed in the results section in the restriction of inference of the study results upon the general HIV positive infant population. However as this study aims to address outcomes in routine care setting this bias will at least partly reflect guideline changes (i.e earlier infant ART initiation recommended in later years). The bias is therefore indicative of the current programmatic characteristics of infant HIV testing and ART initiation.

Loss to Follow Up

LTFU shall be defined where the last visit recorded is more than 9 months prior to site database closure with the date of LTFU being the date of the last visit. Ascertainment bias may occur, as unidentified death may be the reason for the program attrition.

Confounders

Assessment of potential confounders will be made in the analysis. Adjustment for confounders will be done by use of multivariate regression methods in the data analysis where appropriate. This is a retrospective analysis of prospectively collected cohort data and thus assessment and adjustment of confounders is limited to those confounders measured in the primary data capturing. This may result in residual confounding. Time based confounding will not be assessed for purposes of the dissertation.

Missing data

Patterns of missingness will be assessed and if appropriate methods of multiple imputation shall be used according to this pattern so as to minimize bias associated with complete case analysis (49, 50).

Data Analysis

Analysis of pooled cohort data from infant ART sites that has been merged using the agreed IeDEA-SA format. For all analyses, techniques will be used that account for between cohort variation. The data shall be analysed using STATA statistical software version 12 (51).

Key components of the analysis plan will be:

Descriptive analysis

The baseline characteristics of infants starting ARV's will be described using means and standard deviations for normally distributed continuous variables and medians Interquartile Ranges for non-normally distributed continuous variables. Frequency and proportions shall be used to describe categorical variables. Longitudinal profiles of response variable will be represented graphically and with summary statistics. These will include both mean profiles over time for numerical variables (such as CD4 count and percentage) and changes in proportions for categorical variables (such as proportion with HIV-RNA <400 copies/ml) and those numerical variables where categorisation is appropriate.

Survival analysis

Estimation of median time from ART start in an HIV-infected infant to death, LTFU, TFO and virological suppression will be done using the Kaplan-Meier method. Crude and adjusted associations between baseline characteristics and ART outcomes will be done using Cox Proportional Hazards models for survival analysis of

Mortality and time to virological suppression. Competing risk analysis shall additionally provide cumulative incidence functions for death, LTFU and TFO.

Additional Analytic Procedures

Multiple imputation of baseline characteristics as a method for managing missing information shall be done if and where found appropriate and will use the STATA 12.0 (51) ICE program and Rubin's Rules to attain pooled estimates of imputed data sets. A post-imputation model selection method of assessing variable importance (VI) will provide a model and estimates in addition to those from an a priori model.

The detailed analysis plan for the infant epidemiology concept has been circulated to the working group of IeDEA-SA **(Appendix B).**

Ethics

Ethical Approval

The parent protocol: The IeDEA –SA (previously known as The Observational Antiretroviral Studies in Southern Africa (OASIS) Collaboration) collaboration has received University of Cape Town **(Appendix D and Appendix E FHS017)** and University of Bern, Switzerland approval (HREC Reference 084/2006). The data to be used for this analysis are obtained from individual IeDEA sites each of which has existing local institutional review board or Human Research Ethics Committee approval for collection of data and contribution of data to IeDEA-SA collaborative analyses (46).

Risk classification

As a project involving the secondary analysis of data already collected at the primary sites and collated the proposed analysis is classified as having minimal risk.

Potential risks and discomforts

Use of this anonymised data for secondary data analysis holds no foreseen direct risk or harm to those whose information has routinely been collected for primary purposes, as all data is anonymised prior to transfer to the IeDEA-SA Data Centres and the analyses require no direct contact with participants at individual cohorts.

Potential Benefits

The potential benefit of the proposed research is the opportunity to gain an understanding of the individual and programmatic characteristics of routine care in

Southern Africa and thus to provide the evidence necessary to advise optimal infant care and management in this setting. It thus additionally offers the possibility of a societal benefit and a benefit to future infants initiating ART in this setting.

Consent, Privacy and Confidentiality

Data used for this study is fully anonymised and stripped of identifiers at the site level and due to this individual consent is not required where de-identified data is used (46). Password protected encryption and compression is used for the transfer and storage of data. The encryption password (minimum of 10 characters long, including upper/lower case, numbers and special characters) is communicated to the relevant data centre contact person by fax or by telephone, and not by email. Importation and merging of data is done by a dedicated IeDEA-SA data manager into a secure instance on an enterprise SQL Server database. Security is ensured through user level and network access control.

Involvement of vulnerable persons

The inclusion of individuals under the age of 18 years, as will be done in the study, constitutes the involvement of vulnerable persons. The inclusion of this age group in the study is necessitated, as they themselves are the group for whom this evidence is needed. Use of other age groups for inference upon this group cannot be made as described earlier in the background section. Further support for the inclusion of this age group is, as highlighted earlier, in the paucity of literature and research attention as described by the DNDi (3). The anonymisation and protection of data shall ensure the protection of these participants and the minimisation of harm including stigmatisation and discrimination associated with HIV infection.

Stakeholders

Stakeholders include members of the IeDEA international and Southern African groups, Site Investigators, Facility Managers at participating sites as well as infants and caregivers attending those sites, policy makers in the relevant settings and members of the academic community.

Dissemination of Results

The findings of this study shall be disseminated to the stakeholder's through internal reports, reports back to participating sites, submission of abstracts to appropriate academic meetings and conferences as well as to relevant peer-reviewed journals for publication.

Logistics

Timetable

Table 4 below describes the proposed study time and outlines the expected time requirements for completion of necessary tasks related to the research and development of the final dissertation.

Table 4. Timetable for completion of mini-dissertation

Task	Expected date of completion
1 Protocol Development	
1.1 Draft Protocol	August 2013
1.2 Draft to Supervisors	September 2013
1.3 Feedback for Revision	October 2013
1.4 Submission for expedited Review	April 2014
1.4 Submission for Departmental Approval	April 2014
2 Literature Review	
2.1 Systematic Search	June 2013
2.2 Write Up	August 2013
3 Data Management and Analysis	
2.1 Data Cleaning	January 2014
2.2 Data Analysis	April 2014
4 Write-Up	
4.1 Draft Manuscript	May 2014
4.2 Draft dissertation to UCT Supervisors	May 2014
4.3 Feedback for Revision	June 2014
4.4 Finalise Dissertation	June 2014
5 Submissions	
5.1 UCT Submission	June 2014
5.2 Journal Submission	July 2014
6 Results Dissemination	
6.1 Communication to stakeholder	June 2014

Budget

There are no foreseeable budgetary requirements as a retrospective secondary data analysis shall be conducted and the questionnaire forms part of routine IeDEA site survey data. The IeDEA-SA project is already funded and Mireille Porter's time working on the analysis will be funded by the IeDEA-SA project.

Contact Details

Author: Mireille Porter

CIDER, School of Public Health and Family Medicine

Tel: 021 406 6808

Email: mireilleporter@gmail.com

Address: CIDER Room 5.53 School of Public Health and Family Medicine, Falmouth Building, Faculty of Health Sciences, University of Cape Town

Supervisor: Dr Mary- Ann Davies

CIDER, School of Public Health and Family Medicine, University of Cape Town

Tel: 021 406 6051

Fax: 021 406 6764

Email: mary-ann.davies@uct.ac.za

Address: CIDER Room 5.39 School of Public Health and Family Medicine, Falmouth Building, Faculty of Health Sciences, University of Cape Town

Co-Supervisor: Professor Brian Eley

School of Child and Adolescent Health, University of Cape Town

Email: brian.eley@uct.ac.za

Red Cross Children's Hospital

References

1. UNICEF. HIV and AIDS. Eastern and Southern Africa. . 2013 [updated 2012; cited 2013 14 October]; Available from: http://www.unicef.org/esaro/5482_HIV_AIDS.html.

2. World Health Organisation. Early detection of HIV infection in infants and children. Guidance note on the selection of technology for the early diagnosis of HIV in infants and children. Summary of recommendations. 2007: Available from: http://www.who.int/hiv/paediatric/EarlydiagnostictestingforHIVVer_Final_May07.pdf.

3. DNDi. Drugs for Neglected Diseases Initiative. 2013 [cited 2013 14/06/2013]; Available from: http://www.dndi.org/diseases-projects/diseases/paediatric-hiv.html.

4. Chiappini E, Galli L, Tovo P-A, Gabiano C, Gattinara GC, Guarino A, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. Official Journal of the International AIDS Society. 2006;20(2):207-15.

5. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. New England Journal of Medicine. 2008;359(21):2233-44.

6. World Health Organisation. Antiretroviral Therapy For HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a public

health approach. 2010 revision2010: Available from: http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf.

7. UNAIDS. Report on the global AIDS epidemic 2010: Available from: http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf.

8. World Health Organisation W. Fact Sheet HIV/AIDS no 360 [serial on the Internet]. 2012; (22/07/2013): Available from: http://www.who.int/mediacentre/factsheets/fs360/en/index.html.

9. UNICEF. Towards an AIDS-Free Generation 2012: Available from: http://www.unicef.org/aids/files/hiv_InfographicREV2.pdf.

10. World Health Organisation W. Children are not little adults, Children's Health and the Environment. WHO Training Package for the Health Sector2008: Available from: http://www.who.int/ceh/capacity/Children_are_not_little_adults.pdf.

11. Puthanakit T, Bunupuradah T. Early versus deferred antiretroviral therapy in children in low-income and middle-income countries. Curr Opin HIV AIDS. [Review]. 2010 Jan;5(1):12-7.

12. UNAIDS. Progress Report on the Global Plan2013 22/07/2013]: Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20130625_progress_global_plan_en.pdf.

13. Newell M-L, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. The Lancet. 2004;364(9441):1236-43.

14. Ahoua L, Guenther G, Rouzioux C, Pinoges L, Anguzu P, Taburet AM, et al. Immunovirological response to combined antiretroviral therapy and drug resistance patterns in children: 1- and 2-year outcomes in rural Uganda. BMC Pediatrics. 2011;11:67.

15. L'Homme R, Warris A, Gibb D, Burger D. Children with HIV are not small adults: what is different in pharmacology? Curr Opin HIV AIDS. 2007 Sep;2(5):405-9.

16. Dunn DG, D.M; Duong, T Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. The Lancet. 2003;362(9396):1605-11.

17. Prendergast A, Mphatswe W, Tudor-Williams G, Rakgotho M, Pillay V, Thobakgale C, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. Official Journal of the International AIDS Society. 2008 Jul 11;22(11):1333-43.

18. Tukei VJM, M; Asiimwe, A.R; Migisha, D; Maganda, A; Bakeera-Kitaka, S; Kalyesubula, I; Musoke, P and Kekitiinwa, A. Virologic, immunologic and clinical response of infants to antireteroviral therapy in Kampala, Uganda. BMC Pediatrics. 2013;13(42).

19. Berk DR, Falkovitz-Halpern MS, Hill DW, Albin C, Arrieta A, Bork J, et al. Temporal Trends in Early Clinical Manifestations of Perinatal HIV Infection in a Population-Based Cohort. Journal of the American Medical Association. 2005;293(18):2221-31.

20. McGrath CJ, Chung MH, Richardson BA, Benki-Nugent S, Warui D, John-Stewart GC. Younger age at HAART initiation is associated with more rapid growth reconstitution. Official Journal of the International AIDS Society. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. 2011 Jan 28;25(3):345-55.

21. Luzuriaga K, McManus M, Mofenson L, Britto P, Graham B, Sullivan JL. A Trial of Three Antiretroviral Regimens in HIV-1–Infected Children. New England Journal of Medicine. 2004;350(24):2471-80.

22. Mphatswe W, Blanckenberg N, Tudor-Williams G, Prendergast A, Thobakgale C, Mkhwanazi N, et al. High frequency of rapid immunological progression in African infants infected in the era of perinatal HIV prophylaxis. Official Journal of the International AIDS Society. 2007;21(10):1253-61.

23. Laughton B, Cornell M, Grove D, Kidd M, Springer PE, Dobbels E, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. Official Journal of the International AIDS Society. [Comparative Study Randomized Controlled Trial Research Support, N.I.H.]. 2012 Aug 24;26(13):1685-90.

24. Shiau S, Arpadi S, Strehlau R, Martens L, Patel F, Coovadia A, et al. Initiation of Antiretroviral Therapy Before 6 Months of Age is Associated with Faster Growth Recovery in South African Children Perinatally Infected with Human Immunodeficiency Virus. J Pediatr. 2013 Jan 10.

25. World Health Organisation. Report of the WHO Technical Reference Group: WHO Antiretroviral Therapy for Infants and Children 2008 ,2008: Available from: http://www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf.

26. World Health Organisation W. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection2013: Available from: http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html.

27. World Health Organisation. Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector2010; (05/08/2013): Available from: www.who.int/hiv/pub/2010progressreport/summary_en.pdf.

28. Johnson LF, Davies MA, Moultrie H, Sherman GG, Bland RM, Rehle TM, et al. The effect of early initiation of antiretroviral treatment in infants on pediatric AIDS mortality in South Africa: a model-based analysis. The Pediatric Infectious Disease Journal. [Research Support, Non-U.S. Gov't]. 2012 May;31(5):474-80.

29. Lallemant M, Chang S, Cohen R, Pecoul B. Pediatric HIV — A Neglected Disease? New England Journal of Medicine. 2011;365(7):581-3.

30. Leroy V, Malateste K, Rabie H, Lumbiganon P, Ayaya S, Dicko F, et al. Outcomes of antiretroviral therapy in children in Asia and Africa: a comparative analysis of the IeDEA pediatric multiregional collaboration. J Acquir Immune Defic Syndr. 2013 Feb 1;62(2):208-19.

31. World Health Organisation. Global HIV/AIDS response: Epidemic update and health sector progress towards Universal Access 2011 Progress Report2011: Available from: http://www.who.int/hiv/pub/progress_report2011/en/.

32. Lilian RR, Kalk E, Bhowan K, Berrie L, Carmona S, Technau K, et al. Early diagnosis of in utero and intrapartum HIV infection in infants prior to 6 weeks of age. J Clin Microbiol. [Evaluation Studies Research Support, N.I.H., Extramural, Non-U.S. Government]. 2012 Jul;50(7):2373-7.

33. Davies M-A. Outcomes and effectiveness of antiretroviral therapy for HIV-infected children in Southern African treatment cohorts. Unpublished thesis presented for the degree of Doctor of Philosophy In the School of Public Health and Family Medicine University of Cape Town. 2013.

34. Hsiao NY, Stinson K, Myer L. Linkage of HIV-infected infants from diagnosis to antiretroviral therapy services across the Western Cape, South Africa. PLoS ONE. 2013;8(2):e55308.

35. Bourne DE, Thompson M, Brody LL, Cotton M, Draper B, Laubscher R, et al. Emergence of a peak in early infant mortality due to HIV/AIDS in South Africa. Journal of the International AIDS Society. 2009 Jan 2;23(1):101-6.

36. Lilian RR, Kalk E, Technau KG, Sherman GG. Birth Diagnosis of HIV Infection on Infants to Reduce Infant Mortality and Monitor for Elimination of Mother-to-Child Transmission. Pediatric Infectious Diseases Journal. 2013 Apr 9.

37. Prendergast AJ, Penazzato, M., Cotton, M., Musoke, P., Mulenga, V., Abrams, E.J., Gibb, D.M.,. Treatment of Young Children with HIV Infection: Using Evidence to Inform Policymakers. PLoS Med 2012;9(7):e1001273.

38. World Health Organisation W. Antiretroviral therapy of HIV infection in infants and children Recommendations for a public health approach (2006 revision)2006: Available from: http://www.who.int/hiv/pub/paediatric/infants/en/index.html.

39. IeDEA-SA. International Epidemiologic Databases to Evaluate Aids Southern Africa. [14/06/2013]; Available from: http://www.iedea-sa.org/index.php?id=2732.

40. Grimsrud AT, Cornell M, Egger M, Boulle A, Myer L. Impact of definitions of loss to follow-up (LTFU) in antiretroviral therapy program evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU. Journal of Clinical Epidemiology. 2013 Jun 14.

41. Hoskins S, Weller I, Jahn A, Kaleebu P, Malyuta R, Kirungi W, et al. An appraisal of indicators used to monitor the treated population in antiretroviral programmes in low-income countries. Official Journal of the International AIDS Society. 2010 Nov 13;24(17):2603-7.

42. Judd A. Early antiretroviral therapy in HIV-1-infected infants, 1996-2008: treatment response and duration of first-line regimens. Official Journal of the International AIDS Society. [Comparative Study]. 2011 Nov 28;25(18):2279-87.

43. Kay J, Wanzira H, Sandison T, Kakuru A, Bigira V, Kamya M, et al. Virologic suppression in nevirapine-exposed HIV-infected infants initiating antiretroviral therapy in rural Uganda. J Trop Pediatr. [Research Support, N.I.H., Extramural, Non-U.S. Goverment, U.S. Government, P.H.S.]. 2012 Jun;58(3):194-9.

44. Luzuriaga K MM, Catalina M, Mayack S, Sharkey M, Stevenson M, Sullivan JL. Early therapy of vertical human immunodeficiency virus type 1 (HIV-1) infection: control of viral replication and absence of persistent HIV-1-specific immune responses. Journal of Virology. 2000;74(15):6984-91.

45. Faye A, Le Chenadec J, Dollfus C, Thuret I, Douard D, Firtion G, et al. Early versus deferred antiretroviral multidrug therapy in infants infected with HIV type 1. Clin Infect Dis. 2004 Dec 1;39(11):1692-8.

46. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P, et al. Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol. 2012 Oct;41(5):1256-64.

47. IeDEA. The International Epidemiologic Database to Evaluate AIDS Web Page. NIH; [12/07/2013]; Available from: http://www.iedea.org.

48. Fenner L, Brinkhof MW, Keiser O, Weigel R, Cornell M, Moultrie H, et al. Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa. Journal of Acquired Immune Deficiency Syndrome. 2010 Aug;54(5):524-32.

49. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Statistics in Medicine. 1999 Mar 30;18(6):681-94.

50. Patrician PA. Multiple imputation for missing data. Research in Nursing and Health. 2002 Feb;25(1):76-84.

51. StataCorp. STATA 12. In: StataCorp, editor. Texas: StataCorp LP; 2011.

PART B: LITERATURE REVIEW

Table of Contents

Introduction 4

Background 4

Aim and Objectives 5

Review Process 7

Structure of the Review 7

Search Strategy 7

Inclusion Criteria 8

Exclusion criteria 8

Articles Published 9

Quality and Comparability of Studies 10

Primary aims and focus of the study 10

Study Designs 11

Infant subgroup definition 11

Sample Size 11

Follow Up 11

Study Population and Inclusion Criteria 12

Infant initiation guidelines 13

Confounders 14

Missing Data 15

Results 22

Baseline Characteristics 22

Age 22

Virological 23

Immunological 23

Clinical disease 24
Growth 25
PMTCT exposure 26
Cotrimoxazole Prophylaxis 27
Tuberculosis 28
Regimen 28
Initiation delay 29
Other Baseline Characteristics 29
Outcomes 34
Mortality 34
Virological Outcomes 36
Immunological Outcomes 37
Clinical Outcomes 38
Growth Measures 38
Loss to Follow Up 39
Loss to Program 41
Other 42
Determinants of infant outcomes 47
Summary, Interpretation and needs for further research 50
References 57

List of Tables

Table 1a. Quality and Comparability - Analytic Studies 16

Table 1b. Quality and Comparability - Descriptive Studies 17

Table 2a. Infant subgroup measurements and Validity – Analytic 19

Table 2b. Infant subgroup Measurements and Validity – Descriptive 20

Table 3a. Baseline Characteristics – Analytic 31

Table 3b. Baseline Characteristics – Descriptive 32

Table 4. Loss to Program Outcomes 42

Table 5a. Outcomes described – Analytic Infant Outcomes 44

Table 5b. Outcomes described- Descriptive infant outcomes 45

Table 6. Determinants of infant outcomes 49

List of Figures

Figure 1: Flow chart showing the identification of published articles and inclusion in the review. 9

Introduction

Background

The expansion of programs providing antiretroviral therapy (ART) to those living with the Human Immunodeficiency Virus (HIV) in Sub-Saharan Africa is said to be "one of the largest pharmacologic interventions to promote health to date" (1, 2). The call for an increases velocity and coverage of ART provision for infants living with HIV was formalised in the 2008 World Health Organisation (WHO) infant and children ART guidelines with recommendation for the initiation of ART for all HIV positive infants immediately upon diagnosis regardless of the immunological and clinical disease criteria previously used (3). Although catalysed by experimental evidence from The Children with Human Immune Deficiency Virus Early Antiretroviral Therapy Trial (CHER) (4) these changes occurred upon a background of observational studies whose contribution of evidence for the early initiation of ART in infancy is not insignificant (5-9).

The CHER study, a South African trial looking at early versus deferred ART initiation in infancy, provided evidence in support of early diagnosis and treatment of HIV infected infants from a sample of infants with an average age at commencement of ART of seven weeks, complete availability of appropriate laboratory testing and drug regimens including protease inhibitors, minimisation of loss to follow up (LTFU) and the exclusion of those with comorbid conditions or severe immunosuppression (4).

Within Sub-Saharan Africa, and with Southern Africa in particular considered as the epicentre of the global HIV burden (10), both the short term impact and long term outcomes of policies and programs for ART roll-out are met with obstacles and trials

pertaining to the resource-scarce setting of this area (11, 12). In a region where the 'routine-setting' is characterised by concerns of delayed and missed testing, poor follow up, non-adherence, limited resources and restricted laboratory access further complicated by the social, diagnostic, monitoring and treatment needs of infants there exists a severe contrast between that setting within which experimental evidence forming these policies was gained and the setting which these infants in reality exists (13-18) .

Examination of literature describing findings from observational studies in Sub-Saharan Africa which involve an HIV infected infant population group on antiretroviral therapy may provide us with opportunity to gain insight into the characteristics of these infants, their outcomes and the predictors of these outcomes within routine care settings of resource scarce environments.

Aim and Objectives

The aim of this literature review is to review current literature so as to place the proposed study within a context of up-to-date academic evidence appropriate to the objectives and methods of the mini-dissertation. Furthermore the aim is to critically assess those studies identified regarding their availability and quality – specifically their ability to provide valid conclusions- and in doing so to identify areas where further research, including the proposed study, might be justified.

This review seeks to address the objectives of the mini-dissertation. These objectives are as follows:

1. To describe the baseline characteristics of infants commencing ART in the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) sites.

2. To describe and examine the outcomes of infants starting ART in Southern Africa.

3. To identify and examine predictors for these outcomes.

The Objectives of the structured review therefore stand as follows:

1. To identify all published literature pertaining to studies assessing the outcomes (and where available the predictors of these outcomes) of infants initiated on ART in routine care in Sub-Saharan Africa,

2. To consider the evidence provided by the literature regarding all three objectives of the mini-dissertation,

3. To review and report on the quality and results of the studies by critically reading and synthesising the findings and evidence regarding the outcomes of these infants, and

4. To synthesise this information and to identify areas where further research would be useful.

Review Process

Structure of the Review

The review shall present the process of the identification of literature and the assessment of the quality and comparability of the identified literature. Following this a discussion of the findings of these studies – in categories of baseline characteristics, outcomes and predictors of the outcomes- shall be presented with further discussion of resulting issues of validity therein. The review shall conclude, in keeping with the above review objectives, with a summary of the information gained from these studies and propose a way forwards regarding the study of the mini-dissertation.

Search Strategy

The online PubMed Interface (19) was used to search the Medline bibliographic database using the following key word search:

(infant OR "under 1 year old*" OR "under-1" OR "young children") AND

(antiretroviral* OR ART OR HAART OR ARV*) AND

(HIV OR AIDS OR human immunodeficiency virus OR acquired immune deficiency syndrome) AND

(outcome* OR response OR mortality OR survival OR benefit OR effect OR effectiveness OR health OR suppression)

NOT pregnancy NOT pregnant NOT maternal NOT maternity NOT PMTCT NOT cure

(*HAART: Highly active antiretroviral therapy, PMTCT: Prevention of Mother to Child transmission of HIV, ARV: Antitretroviral)*

Inclusion Criteria

- Articles from Sub-Saharan Africa reporting on outcomes of starting first-line ART (minimum of three antiretroviral agents) in infancy. A cut-off of group definition of below 18 months was used. This age inclusion criteria was set in view of the severe paucity of literature pertaining to predictors of infants ART outcomes for a population initiating under 12 months of age.

- The outcomes included were survival/mortality, immunological, virological and clinical disease status, growth or nutrition and opportunistic infections as well as loss to follow up, transfer out, adherence, regimen change and resistance.

- Those studies where the study design is observational were included and priority given to cohort, case-control and cross-sectional designs. Both descriptive and analytic studies were included.

- Priority was given to literature published in the past 10 years (January 2004 up to August 2013)

Exclusion criteria

- Studies which included infants as part of a wider spectrum of ages but did not provide a separate description and/or analysis of the outcomes of these infants (allowed categorisation < 18 months) were excluded.

- Those studies including less than 25 infants were excluded from the review.

- Studies where the majority of participants were either on regimens using less than three ART medicines or second-line therapy were excluded.

- Those studies only observing highly specific outcomes not directly pertaining to our study objectives were excluded. This included studies investigating malaria, lipid profile responses, genetic mutations and nephrotoxicity.

- No quality criteria besides number of infants were used to determine exclusion. Included studies were however assessed for quality as discussed in the next section.

Titles, published abstracts, methodology, results sections and, where necessary for clarity, the full text of identified articles were read by the author and the above inclusion and exclusion criteria applied. In addition the bibliographies of reviews of the initiation of ART in infancy (from original PubMed search) were examined and studies found to be in agreement with the above criteria were added.

Articles Published

The search as described above yielded 998 published articles, 18 of which satisfied the inclusion and non-exclusion criteria **(Figure 1)**. A further article (20), meeting the same inclusion criteria, was identified through examining bibliographies of reviews and articles identified. A study done by Kay et al (2012) was further included despite its inclusion of one child of 19 months of age (21). This was done in view of the severe paucity of literature pertaining to the outcome virological suppression and the importance of the contribution of evidence as provided by this study.

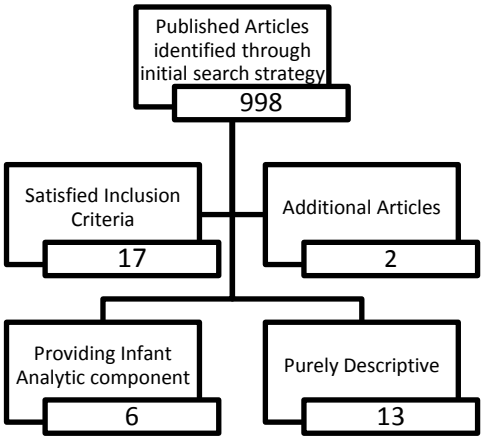


Figure 1. Flow chart showing the identification of published articles and inclusion in the review.

Quality and Comparability of Studies

The key features regarding quality and comparability of the studies are shown in **Tables 1a and 1b** collated as per inclusion of analytic and descriptive information respectively. Quality criteria assessed for purposes of this review included primary aim and focus of the study (with reference to population group), study design, sample size (including proportion of infants) and inclusion and exclusion criteria. Comparability criteria include the year of study, presiding guidelines used for ART initiation, definition of infant subgroup and follow up time. Furthermore this section will include a review of the variables measured and the management of incomplete and missing outcomes.

Primary aims and focus of the study

Of the 19 studies included in this review only three were entirely comprised of an infant cohort (16, 21, 22). In keeping with the inclusion criteria all studies identified outcomes (one or more) of children initiating ART and the vast majority (16 of 19) of studies provided a minimum of one baseline measure at ART initiation for their infant participants. The six analytic studies looked at the predictive ability of one or more of these baseline characteristics for the outcomes assessed. Two of the six analytic articles were however presentations of different aspects of the same study but both were included as they each presented different outcome measures (23, 24). Two further studies (Davies et al (2009) and Fenner et al (2010) overlapped regarding the study population and outcomes observed as both provide descriptive information on mortality in infants from the IeDEA-SA cohorts in similar time periods(25, 26). The remaining 13 studies, although almost all analytic in their

overall design for the total paediatric cohort, provided only outcome information of a descriptive nature for the infant subgroup **(Figure 1)**.

Study Designs

All studies as per inclusion criteria were observational studies and the vast majority of these were cohort studies (prospective and/or retrospective).

Infant subgroup definition

A threshold of less than 18 months for classification as an infant was used in over half of the studies. Only one study, having initially been designed to include only those up to 18 months, included infants up to 20 months due to delays in initiation processes (21). The possible implications of the age of cohorts are considered in the section on quality and comparability of results. The remaining studies used a threshold of less than 12 months with one of these being further subdivided into less than six months and six-12 months (27).

Sample Size

None of the studies included the use of sample size calculations but rather aimed to include as many participants as could be identified and who met inclusion criteria. The range of infant group sample sizes was 34 – 2151. The proportion of infants in the studies involving a total cohort of a wider age range were a minimum of 2% (n=36) (28) and a maximum of 44.7% (29) of all children in the study.

Follow Up

Follow up time was only specified for the infant subgroup in two studies with medians of 12.3 months (approximately 370 days) (30) and 752 days (16). In those

studies reporting an overall cohort median follow up time, this ranged from 196 days to 820 days (27, 31).

Study Population and Inclusion Criteria

All studies, as per inclusion criteria, were conducted within Sub-Saharan Africa. The study by Sauvageot et al (2010), although being conducted in Asia concurrently, provided separate result pertaining specifically to the African cohort (32). In keeping with the inclusion criteria all studies only included infants non-exposed to ART beyond Prevention of Mother to Child transmission of HIV (PMTCT) who were initiating a first line regimen of a minimum of three ART drugs.

Despite the observational nature of all studies and an often stated benefit of capturing routine setting/standard care outcomes there was significant variation in the inclusion criteria beyond programmatic requirements of age and drug experience. These were largely for analysis purposes and related to risk of program attrition such as geographical proximity, caregivers, minimum follow up times and site sizes. Feinstein et al (2012) only included those who were defined as stunted or underweight at baseline and Kay et al (2012) only included those who had experienced nevirapine exposure (maternal or infant) prior to initiation of ART and had at least 1 viral load measurement after ART initiation (21). Further inclusion criteria were full attendance of visits as well as a 95% adherence at six weeks (33), having completed six months of ART (22) and identification of a parent or guardian as well as proximity to the facility, willingness to be visited at home and being over the age of six weeks (16).

All sites included in the studies, including non-governmental, provided free routine care. This is important in decreasing the risk of selection bias resulting from

preferentially providing access to those of higher socioeconomic status. The exclusion of orphans in the Tukei et al (2013) study not only decreases the external validity of these findings in areas where orphanhood is prevalent but also runs the risk of introducing selection bias as these infants have been shown in other studies to be at greater risk of delayed initiation, increased severity of clinical stage and at higher risk of worse outcomes (34). The exclusion of those living beyond 20km of the facility in this study may also result in selection bias as children from rural areas have been shown to have delayed initiation, lower baseline immunological status and poorer outcomes including higher loss to follow up (35). The effect of population selection on the interpretation of any characteristics or outcomes observed in the study is of concern as these criteria reduce the comparability of the populations and the ability to compare the outcomes reported. In particular the implication of selecting a population which is more likely to remain in care when assessing outcomes of death and programmatic end through loss to follow-up is of concern.

Infant initiation guidelines

Due to the length of observation periods almost all studies were affected at a point by changes to WHO and/or national guidelines. Guidelines used were largely those of the WHO or largely comparable National Guidelines. The majority of studies included at least a portion of their infants initiated as per WHO 2006 guidelines and the four most recent studies (16, 27, 29, 36) all included a portion of participants initiating ART in accordance with the 2010 WHO guidelines for early initiation regardless of immunological and clinical criteria under 24 months of age (37).

The study of outcomes of HIV infected infants is particularly vulnerable to the effect of selection bias through the unintentional selection of a group of “survivors”. This

survival bias arises where death due to HIV occurring prior to initiation of ART naturally precludes inclusion within the observed cohort. It is thus directly affected by trends in the age of initiation and the immune and disease status at initiation and therefore by the prevailing initiation guidelines used.

All analytic studies included in this review include more than a single guideline therefore establishing two subgroups with different expressions of this form of bias. Only one study took the guidelines used into account in their analysis however it was not found to have any significant associations with the attainment of virological suppression at six months (16). The same study also discusses the number of infants who died prior to inclusion and although these infants are excluded in analysis it is an important concern in interpreting the final results and understanding the important role of delay in initiation and the impact this can have on virological and mortality statistics.

Confounders

The measurement and management of confounders varied greatly in the analytic studies where a mention of the consideration of known and unknown confounders in analysis was made in some (16, 21) compared to the inclusion of all variables found to be significant in the larger adult and child study in another(23, 24). The possible over adjustment for confounding factors as done in the latter could result in an inappropriate adjustment for mediating factors and a resulting null association when in truth one exists. The failure to measure factors such as comorbid disease, socioeconomic variables, feeding and maternal conditions in the majority of these studies would result in an inability to adjust for their unknown confounding effects and residual confounding (38).

Missing Data

The prevalence of missing data was only described for the infant group in four studies (29, 32, 39, 40). KIDS-ART LINC (2008) was the only study which looked at factors associated with missing data and identified characteristics associated with missingness (younger age and regimen). The management of missing data, where reported, largely involved exclusion from multivariate analysis of those participants with incomplete data sets (22-24, 41). Of note is the exclusion of over 27% of participants by Purchase et al (2012) for incomplete six months outcome data due to loss to program (22). The use of complete case analysis may result in a selection bias as those with complete data may not represent the total population where this missingness is not completely at random (42, 43). The assessment of factors associated with missingness such as in the KIDS-ART LINC (2008) study is necessary to reassure us as to the effect of this exclusion on bias. Multiple imputation, such as used by Fenner et al (2010) (26) is one method which can prevent the exclusion of these participants and improve the validity of the findings if used appropriately (42, 43).

Table 1a. Quality and Comparability - Analytic Studies

Author	Year of Publication	Observation Period	City, Country	Setting	Study design	Infant Subgroup	Infant Sample Size (% total cohort)	Follow up Time	Inclusion Criteria	Initiation guidelines followed
Bolton–Moore et al (2007) (23)	2007	2004-2007	Zambia, Lusaka.	Primary Care Government Clinics	Retrospective cohort	< 18 months	291 (9.9%)	NRI. Infants contributed 213 child-years. Overall: 378[a] days (138 – 692[c])	NR	Changed to WHO 2006 in 2006
Mubiana – Mbewe et al (2009) (24)	2009	2004-2006	Lusaka, Zambia	Primary Care Government Clinics	Retrospective cohort	< 18 months	101 (8%)	NRI. 280 days[a] (110 – 459 [c])	NR	Changed to WHO 2006 in 2006
Purchase et al (2012) (22)	2011	2005-2008	Kwazulu Natal, South Africa	Township	Retrospective cohort	< 12 months	94 (100%)	NR. Observation up to 18 months post-initiation	< 12 months, Completed ≥ 6 months ART, 2 reliable caregivers	Similar to WHO 2006 then stage 2 or CD4<30% after 2007
Feinstein et al (2012) (41)	2012	2004-2008	Johannesburg, South Africa,	Tertiary Facility Outpatient Paediatric Clinic	Prospective cohort	<12 months	676 (28.2%) *Only reported for < 2 year group*	NR. Administrative end 2 years	Stunted (HAZ< -2) or Underweight (WAZ< -2)	SA national guidelines changed to WHO 2006 in 2006
Kay et al (2012) (21)	2012	2007-2008	Tororo, Uganda	Rural	Prospective cohort	< 20 months	34 (100%)	NR. Observation up to 18 months post-initiation	Nevirapine exposure, ≥ 1 viral load measurement	WHO 2006 updated to immediate start in 2008
Tukei et al (2013) (16)	2013	2009-2012	Kampala, Uganda	Outpatient Non-governmental Free clinic.	Prospective cohort	< 12 months	84 (100%)	752 days[a] (531-980 [c])	Living within 20km, accept home visits, parents or guardians, >6 weeks old	WHO 2006 (29.8%) updated to early start in 2010

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available ,WHO: World Health Organisation, ART: Antiretroviral therapy, HAZ: Height-for-age z-score, WAZ: Weight-for-age z-score
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months

Table 1b. Quality and Comparability - Descriptive Studies

Author	Year of Publication	Observation Period	City, Country	Setting	Study design	Infant Subgroup	Infant Sample Size (% total cohort)	Follow-up Time	Inclusion Criteria	Initiation guidelines followed
Bong et al (2007) (33)	2007	2004-2006	Mzuzu, Malawi	Free, Hospital based	Retrospective cohort	< 18 months	37 (8%)	NR. Observation up to 6 months post-initiation	< 15 yrs, 6 weeks adherence >95%, no transfers, full attendance	National guidelines
KIDS-ART LINC (2008) (39)	2008	NR-2007	Multicentre, sub-Saharan Africa	Urban	Retrospective cohort	< 12 months	296 (12.3%) analysis on complete data: 80 (7.6%)	NRI. Overall: 20.3 months[a] (11.7-27.9[c])	< 15 yrs, ≥3 drugs, ≥1 day follow up, 6 months ART. Site ≥ 30 children	NR.
Fetzer et al (2009) (31)	2009	2004-2006	Lilongwe, Malawi	Paediatric HIV clinic	Retrospective case-cohort	< 18 months	55 (21.4%)	NRI. Overall: 196 days[a] (105-310[c])	< 18 yrs, ART naïve.	National guidelines
Davies et al (2009) (25)	2009	1999-2008	Gauteng, Western Cape, Kwazulu Natal, South Africa	Multicentre	Retrospective cohort	< 18 months	1758 (29%)	NRI. Overall 16 months[a] (6-29[c])	≤ 16 yrs, ≥3 drugs. Sites >25 children	National guidelines
Anaky et al (2010) (20)	2009	2004-2007	Abijan, Cote D'Ivoire	Multicentre, NGO program urban and semi-rural	Prospective cohort	< 18 months	145 (15%)	NR	≤15 yrs, ART naïve	WHO 2006
Janssen et al (2010) (40)	2009	2004-2008	Kwazulu Natal, South Africa	Decentralised, rural	cohort	< 18 months	58 (12.2%)	NR. 732 child-years	≤ 15 yrs	Regional. Recurrent hospitalisation/ WHO stage > 1/ CD4 ≤ 35% or <1500cells/mm3
Fenner et al (2010) (26)	2010	1998-2008	South Africa, Malawi, Mozambique, Zimbabwe	Multicentre, only urban	cohort	< 18 months	2045 (24.9%)	NRI. Overall: 17.3 months[a] (8.7-25.7[d])	< 16 yrs, ART naïve, ≥3 drugs. Site >100 children	Site dependent: all under 12 months/ immunological and clinical criteria

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available , WHO: World Health Organisation, ART: Antiretroviral therapy, NGO: Non-governmental organisation
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months

Table 1b. Quality and Comparability - Descriptive Studies continued

Author	Year of Publication	Observation Period	City, Country	Setting	Study design	Infant Subgroup	Infant Sample Size (% total cohort)	Follow-up Time	Inclusion Criteria	Initiation guidelines followed
Sauvageot et al (2010) (32)	2010	2002-2008	Multicentre, Sub- Saharan Africa, Asia	MSF free care centres	Prospective cohort	< 12 months	307 (8.5%)	NRI. Overall 10.5 months[a] (3.7-20.6 [c])	< 5 years initiated in MSF program	WHO 2006
Meyers et al (2011) (30)	2011	2004-2008	Soweto, South Africa	Government clinic, township	Retrospective cohort	< 18 months	496 (24%)	12.3 months[a] (3.6-24.8 [c])	<15 years	National guidelines
Ekouevi et al (2011) (28)	2011	2000-2007	West Africa	Multicentre, free ART, urban.	Retrospective cohort	< 12 months	36 (2%)	NRI. Overall: 1761 child-years.	≤ 15 years, Triple ART.	National guidelines
Kabue et al (2012) (27)	2012	2004-2009	Malawi, Lesotho, Swaziland	Multicentre	Retrospective cohort	< 6 and 6-12 months	537 (23%) (119 < 6 months, 299 6-12 months)	NRI. Overall: 2.3 years[a] (1.5–3.1 [c])	< 12 years	National guidelines 2008–2009 all < 12 months.
McNairy et al (2013) (36)	2013	2005-2011	Kenya, Mozambique, Rwanda, and Tanzania	Multicentre, rural and urban	Retrospective cohort	<12 months	2151 (12.1%)	NRI. Overall: 598 days[a] (245-1106[c])	< 15 years	National guidelines From 2007: Unclear. suggests all < 12 months
Omoni et al (2013) (29)	2013	2008-2009	Abuja and Benin, Nigeria,	Hospital- based HIV clinic	Mixed prospective/ retrospective cohort	< 12 months	67 (44.7%)	NR. Observation up to 12 months post-initiation	< 36 months	WHO 2006

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available, ART: Antiretroviral therapy, MSF: Medecins sans frontiers, WHO: World Health Organisation
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months

Table 2a. Infant subgroup measurements and Validity – Analytic Studies

Author	Primary Outcome	Other Outcomes	Baseline Characteristics	Predictors assessed for primary outcome	Definition LTFU	LTFU procedure	Management LTFU
Bolton–Moore et al (2007) (23)	Mortality rate overall, < 90 days, ≥90 days	WAZ, CD4 (%, count), Hb	Age, sex, WAZ, CD4 (%, count), WHO stage, Hb, TB	CD4%, WAZ, Hb, sex, TB, Creatinine, WHO stage, regimen, adherence.	≥ 30 days late & no established death/transfer	Electronic Monitoring with home visits for non-attenders >10days	Reported at time points. Excluded from analysis.
Mubiana – Mbewe et al (2009) (24)	Incident clinical conditions	None	Sex, WAZ, CD4%, WHO stage, Hb	Hb, sex, WAZ, CD4%, WHO stage.	As above	As above	As above
Purchase et al (2012) (22)	Completion of 6,12 and 18 months of ART	WAZ, CD4%, VL, Hb, admissions, BCG IRIS	Age, sex, WAZ, CD4%, VL, WHO stage, TB, admissions, NVP exposure, INH prophylaxis, ART regimen	WHO stage, CD4%, VL, WAZ.	NR	None	Analysis for predictors of loss to program
Feinstein et al (2012) (41)	Weight and Height recovery	LTFU	WAZ, HAZ	CD4	Last seen ≥ 3 months before administrative end and non- event or death	NR	Sensitivity analysis for LTFU/death effect supported null-associations
Kay et al (2012) (21)	Virological suppression at 18 months of ART	CD4%, regimen changes	Age, sex, WAZ, CD4%, VL,WHO stage, NVP exposure, breastfeeding	Age, CD4, VL, weight, sex, WHO stage, breastfeeding	NR	NR	NR
Tukei et al (2013) (16)	Virological suppression at 6 months of ART	Mortality rate, CD4%, adverse events, WAZ, HAZ	Age, sex, WAZ, HAZ, CD4%, VL, TB, time to start, guideline, regimen	Age, Sex, CD4%,, WHO stage, WAZ, HAZ, WHO guidelines, PI regimen	NR	NR	Unclear

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available, ART: Antiretroviral therapy, WAZ: Weight-for-age - score, HAZ: Height-for-age z-score, VL: Viral Load, TB: Tuberculosis, INH: Isoniazid, Hb: Haemoglobin, LTFU: Loss to follow-up, WHO: World Health Organisation, PI: Protease inhibitor.
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months

Table 2b. Infant subgroup Measurements and Validity – Descriptive Studies

Author	Outcomes	Baseline Characteristics	Definition LTFU	LTFU proceed	Management LTFU
Bong et al (2007) (33)	Mortality cumulative probabilities at 3 and 6 months	Age, sex, weight-for-height, BMI, CD4 (%, count), WHO stage, orphanhood, regimen	NR	NR	Acknowledge underestimation of death
KIDS-ART LINC (2008) (39)	Mortality cumulative probabilities (graphically), LTFU	Age, CD4%, disease severity (WHO stage and weight combined statistic), regimen	Last contact > 6 months before database closure, not known death or TFO.	NR	Sensitivity analysis (death combined with LTFU)
Fetzer et al (2009) (31)	Loss to program	NR	NR	No community tracing	Adjustment for associated baseline factors only reduced precision due to sample size.
Davies et al (2009) (25)	Mortality cumulative probabilities (graphically)	CD4 (%, count)	Last contact > 6 months before database closure	Site based death and TFO ascertainment	NR
Anaky et al (2010) (20)	Mortality cumulative probabilities and rates at 3 months and 12 months, LTFU	Age, sex, WAZ, weight, CD4 (%, count), WHO stage, Hb, TB treatment active and past, cotrimoxazole, regimen	Last contact > 3 months before study end.	Phone calls, home visits by social workers and supporters	NR
Janssen et al (2010) (40)	Mortality rates overall, <90days,>90days , CD4(%, count), VL, Hb, LTFU, Albumin, Transfer Out	Age, sex, WHO stage, CD4(%, count), VL, WAZ, TB, Hb, Albumin	No drug collection > 3 months despite not known to have died or TFO.	Phone calls, home visits by nurse tracker	Sensitivity analysis (using maximum and minimum mortality in those LTFU)

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available , WAZ: Weight-for-age z score, VL: Viral load, TB: Tuberculosis, Hb: Haemoglobin, LTFU: Loss to follow-up, WHO: World Health Organisation, BMI: Body Metabolic Index, TFO: Transfer Out

Table 2b. Infant subgroup Measurements and Validity – Descriptive continued

Author	Outcomes	Baseline Characteristics	Definition LTFU	LTFU proceed	Management LTFU
Fenner et al (2010) (26)	Mortality Rate for 12 months rate	None	Last contact > 6 months before closure date.	Site dependent: phone calls, home visits, counselling	Excluded early defaulters from analysis. Sensitivity analysis based on likely mortality in those LTFU
Sauvageot et al (2010)(32)	Mortality cumulative probabilities (at 12 and 24 months), stage 4 events, drug toxicities and retention in care	Age, sex, WHO stage, CD4%, WAZ, TB (active and past), Hb regimen	Missed scheduled visits for more than 2 months	NR	NR
Meyers et al (2011) (30)	Mortality Rate overall, <90days,>90days, CD4%, VL	Age, sex, WHO stage, CD4% and count, VL, WAZ,HAZ, TB, test to start interval	NR	Phone calls, home visits by full time on-site defaulter tracer	NR
Ekouevi et al (2011) (28)	Mortality cumulative probabilities (6 and 12 months), LTFU, Loss to program	none	Last contact > 6 months from closing date.	Vital status not ascertained	NR
Kabue et al (2012) (27)	Mortality cumulative probability up to 36 months (graphically only) proportion at 12 months, CD4%	CD4%	NR	NR	Assumed to be alive for analysis
McNairy et al (2013) (36)	Mortality cumulative probabilities reported at 12 and 24 months, LTFU, retention	Illness severity as defined by WHO stage and CD4%	No clinic visit for more than 6 months	NR	Retention defined as alive and attending care. Non-retained censored.
Omoni et al (2013) (29)	CD4%	CD4%, breastfeeding	NR	NR	NR

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available , LTFU: Loss to follow-up, WHO: World Health Organisation, WAZ: Weight-for-age z score, HAZ: Height-for-age z score, VL: Viral Load, TB: Tuberculosis, Hb: Haemoglobin. WAZ: Weight-for-age z-score

Results

Table 2 above summarises those baseline characteristics, outcomes and predictors of these outcomes which are reported in the articles identified in this review. **Table 3** below summarises the results of baselines characteristics of infants in the articles in this review.

Baseline Characteristics

All but three studies reported at least one baseline characteristic specifically for the infant population. Immunological measures were the most commonly recorded with other frequently reported baseline characteristics being gender, weight-for-age, disease stage as per WHO criteria (37), viral load and regimen. Less frequent characteristics were previous or current tuberculosis treatment or disease, WHO guidelines used for initiation, year of enrolment, Isoniazid prophylaxis, PMTCT nevirapine exposure, feeding options, height-for-age, orphanhood, cotrimoxazole prophylaxis, albumin and enrolment-to-start time interval.

Age

The median or mean ages for the infant subgroup where provided range from 6.2 months to 14 months (16, 20). These ages are not comparable to the far younger median ages seen in the early initiation arms of experimental studies in Southern Africa (CHER median of 7.4 weeks) (4) nor in the developed world (Chiappini et al (2006)) median of 3.6 months (7)). The older population arising from these observational studies holds several concerns regarding the validity of the findings. Most considerable is the concern for survival bias where an older median age suggests the existence of a cohort of survivors. This survival effect is particularly

important in an infant cohort as not only does early infant HIV-related mortality peak at two to three months of age but also those infants perinatally infected have worse outcomes with high early mortality in comparison to those infected through breastfeeding (21, 44, 45). Furthermore, where maternal PMTCT nevirapine exposure occurs, these late seroconverters are more likely to be infected when the nevirapine-exposed mother has reverted to wild type virus rather than a resistant strain and possibly experience more favourable outcomes on a non- protease inhibitor based regimen (21). The delayed age of initiation of infants seen in these studies therefore results in a cohort of those infants who have survived a period of extremely high risk of mortality and are therefore likely to be a group significantly different to all HIV infected infants.

Virological

In keeping with the unavailability of laboratory services and the lack of viral load measurement in resource-scarce settings due to high cost virological measurements were not commonly reported and where reported often yielded high proportions of missing data of up to 67% of children (40). Where reported viral loads measurement ranges from 4.9 to 6.2 $\log_{10}$ copies/ml.

Immunological

The vast majority of studies included some measure of immune function - whether CD4 percentage, count, both or a summative score of illness combining immunological and clinical characteristics (36). Paediatric ART CD4 cell percentages are often considered a more suitable measure of immunological status than absolute counts in the interpretation of these measures in children of different ages due to the age-related variability seen (46).

Median absolute CD4 cell counts reported range from 642-861 cells and with median or mean percentages ranging from 13% (20) to 20% (16). These results are very different to the CHER trial early ART arm where a median CD4% of 35% was reported and even more so to the median CD4% of 54% in the infants observed in the French Perinatal Cohort study (5). A further four studies provided percentage of infants with CD4% below 25% ranging from 82% (21) to over 91% (32). Missing CD4 data of up to 50% (29) in the infant group and 65% (36) for those under the age of 5 years were reported. Several other studies that described an overall cohort (rather than providing a separate description of infants) reported high prevalence of missing CD4 baseline data (20, 25, 28).

Clinical disease

Use of the WHO classification of disease status was relatively consistent however changes from a three stage to four stage system were applied over the course of 2004 and 2005 at different sites. Only Davies et al (2009) discuss their management of this situation as it pertains to the reporting of their overall cohort, but not infants, and label all participants stage three or four under either system as having "clinically advanced disease" (25). Severe disease, as defined most commonly as WHO stage three or four, was prevalent in over 50% in most studies ranging from 12% in Kay et al (2012) (21) to 100% of infants described as being stage four in Bong et al (2007) (33). Kay et al (2012), where only nevirapine exposed infants were included, had a very healthy population with 0% recorded as WHO stage four and 79% stage one. In view of the immunological and virological markers described for this population these results do not seem to be plausible, especially as a significant portion were commenced under initiation criteria of WHO stage four or immunological criteria and measurement or coding error or missing data needs to be considered. It is a

possibility that confusion occurred regarding the previous three stage WHO criteria but this does not account for the high proportion of stage one. In Bong et al (2007) the high prevalence with wasting in the population might be at least partially responsible for the high levels for stage four disease. The general high prevalence of severe disease reflects not only the high rates of progression in infants and their high risk of mortality but also the limited access to testing and treatment seen in routine settings for this group (39).

The use of "severe clinical status" by KIDS-ART LINC (2008) reflects the quality of data as 65.5% of these measures were missing due to incomplete WHO stage or weight-for-age z-score information. Missing data for infant WHO stage was reported at much lower levels in Janssen et al (2010) (10%) and Sauvageot et al (2010) (13%) (32, 40). Anaky et al (2010) and Ekouevi et al (2011) reported high levels of missing disease status data for their overall paediatric cohorts but did not specify that for infants (20, 28) .

Growth

Baseline weight-for-age z-scores (WAZ) of infants varied greatly with median or mean values ranging from a WAZ of -1.8 to that of -3.7. In addition to these reported measures Kay et al (2012) seems to have a relatively low prevalence of poor nutrition characteristics with only 32% being underweight at WAZ < -2 compared to over 62% < -2 in Tukei et al (2013). Of note is that the lower limit seen in Janssen et al (2010) represents only 76% of the infant population as data is missing for this variable for the remainder. Furthermore Anaky et al (2010), representing the upper limit, state an unqualified "high" level of missing data for weight-for-age.

Baseline height-for-age z-scores (HAZ) were only provided for in two studies which varied quite considerably and weight-for-height z-scores (WFHZ) were measured by Tukei et al (2013) with 33.8% WFHZ <-2 and Bong et al (2007).

The WHO guidelines of 2010 encourage monthly monitoring of growth and nutrition for all HIV positive individuals based not only upon the appropriateness of weight band dosing in children under the age of three years but also as it is a strong indicator for the risk of mortality in paediatric studies (37, 47, 48). Identification of high risk infants through growth and nutritional assessment is called for in light of the metabolic needs, co-morbid infections associated with HIV as well as the effects of nutritional deficiency upon the immune system (8, 49).

PMTCT exposure

PMTCT exposure, whether maternal, infant or both, was very poorly recorded. Beyond Kay et al (2012), where nevirapine exposure was an inclusion criterion, reported PMTCT coverage ranges from 65% of infants exposed to maternal or infant prophylaxis to over 94% of infants completely ART naïve-including PMTCT exposure (32). These are lower proportions compared to the CHER trial where, with infants being specifically identified for inclusion through the PMTCT services, only 16% had had no exposure to PMTCT (4). Davies et al (2009) as a multicentre study within South Africa comment on the poor quality of PMTCT recording and found in their study that over 50% of infants did not even have a recorded exposure status (25) and Kabue et al (2012) report missing PMTCT data for 24% of the overall paediatric cohort. These findings are largely in keeping with global statistics at the time such as an estimated coverage of PMTCT (including the no longer supported monotherapy) of 48% in 2010 (50). Prendergast et al (2012) in a review of current

evidence and its use to inform policy suggest that early infant ART initiation guidelines will only show their true impact when the system of antenatal care, PMTCT and infant care is strengthened (9). The gaps in recording, reporting and actual coverage of PMTCT are considerable and together with the older age at initiation, highlight the possibility of poor linkage with maternal antenatal and PMTCT services to infant testing and care and a reduced benefit of infant ART. Populations of HIV infected infants arising from regions of differing PMTCT coverage may also differ regarding outcomes risk as those who seroconvert despite PMTCT may represent infants infected by an already resistant strain or under conditions of high transmission risk such as high maternal viral loads (21).

Cotrimoxazole Prophylaxis

The low frequency of reports on cotrimoxazole coverage despite mention of prevailing guidelines and an evident acknowledgement of the importance of this prophylactic medication suggest common difficulties in ascertaining its use and implementation pre and post-ART. The proportion of missing data for this variable was only reported for the overall paediatric cohort by Ekouevi et al (2011) wherein one site had a 100% missing data prevalence (28). The benefit of cotrimoxazole as established in paediatric experimental studies in Sub-Saharan Africa such as Chintu et al (2004) (51) and Mulenga et al (2007) (52) include reduction in death, hospital admissions and bacterial infections and thus its use may be responsible for a portion of the beneficial response observed in patients on both ART and cotrimoxazole. It therefore is an important third variable for which failure to measure may result in residual confounding.

Tuberculosis

Prevalence of Tuberculosis and/or treatment thereof differed significantly with regards to proportions in initiation cohort and diagnostic methodology. The lowest measured prevalence of active tuberculosis in infants was 2.8% in a semi-urban Ivory Coast population (20) and the highest prevalence occurred in South Africa with over 40% of infants on tuberculosis treatment at time of ART initiation in Purchase et al (2012) (22). Purchase et al (2012) comment that this high prevalence is likely to be due to the unavailability of diagnostic services and the resulting over diagnosis using clinical criteria (22). The high prevalence in infants in these areas with general high tuberculosis prevalence may be affected by maternal tuberculosis infection, impaired Bacilllus Calmette-Guerin (BCG) response and HIV immune suppression (53). The comparison of proportions of infants diagnosed with tuberculosis and the treatment thereof is difficult as the diagnostic resources and thresholds for treatment vary considerably between settings (54).

Regimen

Protease inhibitors (PI) were available and part of the regular infant regimen in several studies, with the majority of these using lopinavir/ritonavir. These studies were almost all of South African populations reflecting the increased access to PIs in this country. In the Ugandan cohort reported by Tukei et al (2013), the most recent study in this review, there was also access to this regimen (16). The use of PI-based regimens for infants is supported by anticipated better outcomes than those on nevirapine regardless of previous nevirapine exposure (55, 56) particularly in the context of PMTCT nevirapine use. Nevirapines's stability at high temperatures, its

fixed dose combination formulations and low cost, however, make it an attractive alternative (13, 56).

Initiation delay

Although time from diagnostic test to start was not provided, the time between registration at the care facility and initiation was recorded by a few of the studies. Meyers et al (2011) reported a median delay of 4.4 weeks from first visit to initiation and comment that this is faster in infants than that observed in their older counterparts. Sauvageot et al (2010) reports a median delay of 0.9 months. In Tukei et al (2013) a median of 57 days occurred from registration at clinic to start and if disaggregated to that under 2006 and 2010 guidelines,these delays are 69 and 33 days respectively. These delays are not considering the delay in test turnaround time and the true unmeasured delay between the first opportunity for identification and treatment initiation is probably far greater (57, 58).

Other Baseline Characteristics

Baseline haemoglobin levels were reported in several studies with low median levels ranging from 9.1 to 9.7 g/dl. Prevalence of missing data was however high with 38% reported missing in Janssen et al (2010). Infant feeding was poorly reported and definitions unclear and inconsistent with up to 85% infants “breastfeeding” at the time of initiation in Kay et al (2012) and 7% exclusively breastfeeding and 73% mixed feeding in the study by Omoni et al (2013) (21, 29). The differences in reported feeding practices at initiation would depend on prevalent guidelines as well as age at initiation and how well this variable was captured.

Data on social factors were generally lacking with orphanhood reported for infants only by Bong et al (2007) where 11% had lost one parent. Fetzer et al (2009)

described 16% of the paediatric cohort as having lost both parents reflecting the understandable increased risk of maternal mortality as the child ages (31). Orphanhood during infancy may however result in selection bias as it has been found to predict delayed access to ART services resulting in a population less likely to be orphans than the true HIV positive infant population (34).

Table 3a. Baseline Characteristics – Analytic

Author	Age	PMTCT	Cotrimoxazole Prophylaxis	Disease severity	CD4	Viral Load	WAZ	HAZ	Tuberculosis	Hb	Regimen (Most common for infants)
Bolton –Moore et al (2007) (23)	11[a]months (7-14[c] months)	NR	NR	81.6% WHO 3/4	572[a] cells/µl (268-959[c]), 14.7%[a] (10.7-20.5[c]) *(35% missing)*	NR	-2.5[a] (-3.8;-1.1[c]) 39.1% < -3	NR	5.20%	9.1g/dl[a] (8.0-10.3 [c])	AZT or D4T +3TC +NNRTI
Mubiana – Mbewe et al (2007) (24)	NRI, Overall 77[a] months (39-119 [c] months)	NR	NR	87.1% WHO 3/4	15.7%[a] (SD 8.2[f]) 75% ≤20%	NR	- 2.5[a] (2.2[f]) 41.3% < - 3	NR	NRI	83.3% > 8.0g/dl	AZT or D4T +3TC +NNRTI
Purchase et al (2012) (22)	8.6 months (2.1-11.9 [c])	65% NVP exposure	NR	77.2% WHO 3/4 (26.6% stage 3, 48.9% stage 4)	15.4%[a] (0.1-43.4 [d])	6.2 $\log_{10}$ copies/ml[a] (1.4-7.9 [d])	-2.7[b] (1.97[f])	NR	40.4% on treatment at ART initiation	9.7 g/dl[a] (7.2-20.2[d])	D4T +3TC + Lop/Rit (79% of infants)
Feinstein et al (2012) (41)	NRI, Overall 4.6[a] years (1.7-7.6 [c] years)	NR	NR	NRI	NRI	NRI	NRI	NRI	NRI	NRI	D4T + 3TC + Lop/Rit
Kay et al (2012) (21)	8.6[a] months (3.2–19.9[d])	All NVP exposed (maternal, child or both)	NR	12% WHO 3/4 (79% stage 1, 9 % stage 2, 12 % stage 3, 0 % stage 4)	19%[a] (9-36 [d]) 82% ≤25% *(15% missing)*	5.8 $\log_{10}$ copies/ml[a] (3.5-7.0 [d])	32% < -2 WAZ	NR	NR	NR	AZT + 3TC + NVP (PI's unavailable)
Tukei et al (2013) (16)	6.2[a] months (4.04-9.0 [c])	NR	NR	55.6% WHO 3/4 (35.6% Stage 3, 20% stage 4)	20%[b] (15-29[d])	56%[a] <750000 copies/ml	-2.2[a] (-3.89; -1 [c]) 62.7 % ≤ -2	-1.92[a] (-3.05;-1.02 [c]) 39.5% ≤-2	11.9%	NRI	AZT or D4T +3TC + NVP (±52%) or Lop/Rit(±35%)

NR: Not reported, NRI: Not reported for infants, WHO: World Health Organisation, NVP: nevirapine, D4T: stavudine, AZT: zidovudine, 3TC: lamivudine, NNRTI: Non-nucleoside reverse transcriptase inhibitor, Lop/Rit: lopinavir ritonavir, PI: protease inhibitor, WAZ: Weight-for-age z score, HAZ: Height-for-age z score, PMTCT: Prevention of mother to child transmission of HIV, TB: Tuberculosis, Hb: Haemoglobin.
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months

Table 3b. Baseline Characteristics – Descriptive

Author	Age	PMTCT	Cotrimoxazole Prophylaxis	Disease severity	CD4	Viral Load	WAZ	HAZ	TB	Hb	Regimen (Most common for infants)
Bong et al (2007) (33)	3.6-16.9[d] months (12-15.6[c])	NR	NR	100% WHO stage 4	861[a] cells/µl (514.7-1373[c]) 15.2 % (9.5-20.6[c])	NR	NR	NR	NR	NR	D4T + 3TC + NVP (split adult FDC)
KIDS-ART LINC (2008) (39)	8.4[a] months (2.2-12[c])	NR	Overall 35.5%	67.6% "severe clinical status" (WAZ<-3/ WHO 3/4) *(65.5% missing)*	83.6% CD4 cells < 25% or abs < 1500 cells/µl *(16% missing)*	NR	*see baseline disease severity*	NR	Overall 2.5%	Overall 6.3%< 7.5g/dl *(47% missing)*	AZT or D4T + 2nd NRTI + PI (67%)
Fetzer et al (2009) (31)	Overall 5.7[a] years	Overall 13% single infant dose	Overall 19%	Overall 92% WHO stage 3/4	NR	NR	NR	NR	Overall 24% active TB, 25% history TB	NR	D4T + 3TC + NVP
Davies et al (2009) (25)	Overall 42.7[a] months (14.7-82.5[c])	Overall >50% unknown exposure status	NR	Overall 50% WHO stage 3/4	642 cells/µl[a] (280-1132[c]) 16.5%[a] (10.0-23.6[c])	Overall 5.36[a] log_{10}copies/ml (4.74-5.89[c])	Overall -1.89[a] (-3.20- -0.93[c])	Overall -2.39 (-3.37- -1.44)	NR	Overall 12.2% Hb < 8 g/dl	D4T + 3TC + + Lop/Rit
Anaky et al (2010) (20)	14[a] months (9-16.75[c])	34% maternal PMTCT program involvement	65.5% prior and 88.3% with ART	39.3% WHO stage 3/4	714 cells/µl[a] (475.5-1182.5[c]) 13%[a] (9-15.7[c])	NR	-3.7[a] (-5.4; -2.5[c])	NR	2.8% active TB, 2.1% previous treatment	9.2 g/dl[a] (8.3-10[c])	2NRTI's + PI (nelfinavir) (55%)
Janssen et al (2010) (40)	13[a] months (4-17[c])	NR	NR	63.8% WHO stage 3/4 *(10% missing)*	766[a] cells/µl (464-1130[c]) 19%[a] (11-28[c]) *(33% missing)*	4.9 log_{10} copies/ml[a] (3.4-5.9[c]) *(67% missing)*	-1.8[a] (-2.8 - -0.9[c]) *(24% missing)*	NR	28.9%	9.5g/dl[a] (8.4-10.4[c]) *(38% missing)*	D4T +3TC + PI
Fenner et al (2010) (26)	Overall 49[a] months (16-120[c])	NR	NR	Overall 78.4% WHO stage 3/4	Overall 11.6%[a] (7-17[c])	Overall 5.4[a] log_{10}copies/ml (4.81-5.92[c])	Overall 24.6%≤-3	NR	NR	Overall 11.6%<8g/dl	NR

NR: Not reported, ART: Antiretroviral Therapy, WHO: World Health Organisation, D4T: stavudine, AZT: zidovudine, 3TC: lamivudine, NRTI: Nucleoside transcriptase inhibitor, Lop/Rit: lopinavir/ritonavir, PI: Protease inhibitor, WAZ: Weight-for-age z score, HAZ: Height-for-age z score, PMTCT: Prevention of mother to child transmission of HIV, TB: Tuberculosis, Hb: Haemoglobin.
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months

Table 3b. Baseline Characteristics – Descriptive continued

Author	Age	PMTCT	Cotrimoxazole Prophylaxis	Disease severity	CD4	Viral Load	WAZ	HAZ	TB	Hb	Regimen (Most common for infants)
Sauvageot et al (2010) (32)	0.7 years [a] (0.5-0.9[c])	94.5% none	NR	70.7% WHO stage 3 or 4 *(13% missing)*	91.7% CD4 <25%, 10% CD4 < 5% *(45% missing)*	NR	-2.6 [a] (-3.6; -1.3 [c])	NR	3.3% current, 9.5% prior TB	17.4% [a] < 7.5 g/dl	AZT or D4T +3TC +NVP (90%)
Meyers et al (2011) (30)	0.75 years [a] (0.47-1.07[c])	NR	NR	88.8% WHO stage 3 or 4	642 cells/µl [a] (293-1058 [c]) 14% (9-19 [c])	6 $\log_{10}$ copies/ml (5.4-6.46)	-3.18 [a] (-4.52 --1.99 [c])	-3.02 [a] (-4.03--1.79)	32.93%	NR	D4T +3TC + PI (Lop/Rit)
Ekouevi et al (2011) (28)	Overall 5 years [a] (2-9[c])	NR	Overall 27.2%	Overall 19.1% WHO stage 4	Overall 13% [a] (7-19 [c])	NR	NR	NR	NR	NR	Overall 2NRTI +1 NNRTI
Kabue et al (2012) (27)	Overall 3.1 years[a] (1.4–7.1 [c])	Overall 62% none	NR	Overall 69.7% WHO stage 3 or 4	83% CD4< 25% or 1500 cells/µl	NR	Overall 32.8% some malnutrition	NR	NR	NR	Overall AZT or D4T + 3TC + NVP or EFV
McNairy et al (2013) (36)	Overall 4.6 years[a] (1.9–8.3 [c])	NR	NR	2006: 56% , 2011: 18% CD4<25%/ 1500 cells/ml^3/ WHO stage 4	Under 5 years: 15% [a] (10-20 [c]), 67% CD4<25%/ 1500 cells/µl	NR	Overall 33% ≤ -2	NR	NR	NR	Overall 2 NRTI'S + 1 NNRTI (95%)
Omoni et al (2013) (29)	Overall 14.3[a] months (8.3 [f])	NR	NR	Overall 58% WHO stage 3 or 4	14.9% [b] (12.4:17.5[CI]) *(50% missing)*	NR	Overall 50% < -2	Overall 64% < -2	NR	NR	Overall 99.3% D4T or AZT + 3TC +NVP

NR: Not reported, WHO: World Health Organisation, D4T: stavudine, AZT: zidovudine, 3TC: lamivudine, NRTI: Nucleoside reverse transcriptase inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, Lop/Rit: lopinavir/ ritonavir, PI: Protease inhibitor, WAZ: Weight-for-age z score, HAZ: Height-for-age z score, PMTCT: Prevention of mother to child transmission of HIV, TB: Tuberculosis, Hb: Haemoglobin.
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months

Outcomes

Outcomes measured for infants in the studies included in this review, as in keeping with the aims of the mini dissertation, include immunological, virological, clinical, growth and program follow-up and retention measures. **Table 4 and 5** below highlight the results of the main outcomes of these studies.

Mortality

Mortality/survival was the most commonly reported outcome and furthermore was analysed for predictors in one study (23). It was most commonly presented as a rate per 100 child-years or as cumulative probability with Kaplan Meier probabilities for given time points. The use of Kaplan Meier cumulative proportions takes into account the effect of loss to follow up through censoring at different event-based time points and where time to event data involves censoring provides us with a more valid statistic than rates (59). Mortality rates for infants for the overall study period as reported in the studies range from 4.09 deaths per 100 observed child years (Tukei et al (2013)) to 21.1 deaths per 100 observed child years (Bolton-Moore et al (2007)) (16, 23). These two studies not only represent cohorts of different age distributions but also significantly different follow-up times with that of the Bolton-Moore et al (2007) study representing a very short observation time of approximately one year and the Tukei et al (2013) study a long observation time of approximately two years. This would affect the estimated mortality rates as this rate is not constant through time with the majority of infant deaths experienced early such as observed in the studies by Anaky et al (2010), Janssen et al (2010), Meyers (2011) and Bolton-Moore et al (2007) studies where we see a far greater rate of death in this first 90 day after initiation of ART(20, 23, 30, 40). Of interest is that these two extremes closely

mimic those mortality rates reported in the CHER trial in the early and deferred treatments arms respectively (4). One Malawian observational study not included in this review as no infant group data were reported showed a mortality rate of 47 per 100 child year in children under the age of two years but reported very limited information on the age group characteristics (60). Those infants in the Bolton-Moore et al (2007) study represented a very ill population with over 80% WHO stage three or four and a low median weight-for-age. Furthermore the Tukei et al (2013) study, the most recent study in this review, included a high proportion of infants on protease inhibitors. Baseline weight-for-age, CD4 cell measures and WHO stage have each been identified as predictors of mortality in those studies within sub-Saharan Africa involving a cohort of older children (26-28, 33). Further still the use of non-Protease Inhibitors have been found to be associated with mortality in children on ART in experimental studies (55, 56, 61). The distributions of these characteristics in the studies may in part be responsible for the differing measures of frequency for mortality.

Cumulative probabilities for mortality by six months range from 8.9% (28) to 24.3% (33) and that by 12 months from 10.7% (28) to approximately 17.5% (28). Bong et al (2007), with the highest six month probability of death, had a baseline WHO stage four prevalence of 100%. As one of the earlier studies these findings also support evidence for a trend over time in HIV outcomes that is dependent not only on changing guidelines, access to antiretroviral therapy but also possibly to programmatic factors that are more difficult to measure (6, 62).

Further description of mortality statistics according to age group within infancy (27) and year of initiation (36) suggest worse outcomes for those starting prior to six months of age compared to those between the ages of six and 12 months and

improving 24 month survival between 2005 and 2009. These differences are likely to be due to the survival bias discussed earlier and not true worse outcomes. Analyses of the strengths of these associations and their predictive power were however not reported on.

Virological Outcomes

In keeping with the scarcity of baseline virological measures, virological outcomes were measured in only five studies and in only two of these (16, 21) were predictors for this outcome assessed. In addition to absolute measures of HIV-RNA copies, virological outcomes include virological suppression (22, 30), undetectable viral load (22) and virological rebound after suppression (30). Definitions were largely consistent where virological suppression was considered to be viral load <400 copies/mL after ART initiation once or twice at different study observation points and viral rebound was defined as viral load >1000 copies/mL on two subsequent occasions after viral suppression had occurred (30). In the study by Davies et al (2009) attainment of viral load < 400 copies/mL led to definition as "undetectable" however this variable was not reported for infants specifically(25). Cumulative probabilities of achieving virological suppression (viral load <400 copies/ml) varied considerably in the two studies it was reported in (16, 21) possibly reflecting the younger age group and more severe disease staging in the Tukei et al (2013) study. The proportion of infants attaining virological suppression during the study observation period is provided by one study (30) and median viral loads at certain time points reported for 2 others (22, 40). The considerable difference in the median values reported in these two studies may in part be due to the high level of missing data in the Janssen et al (2010) study. Not knowing the reason for non-recording or measuring of virological data means we cannot exclude the possibility that poor

clinical or immunological status may have led to higher likelihood of virological assessment for confirmation of treatment failure thus representing a more ill population than the rest of the cohort and affected the validity if these results.

Virological rebound after suppression is reported in two studies with no rebound occurring at 12 months after ART initiation in those who suppressed in the Tukei et al (2013) study (16) and over 9% of those initially suppressed having virological rebound in Meyers et al (2011) (30).

Immunological Outcomes

Immunological outcomes were reported far more frequently than virological ones. Median/mean CD4 percentages at six months ranged from approximately 23% to 30%, 12 month percentages from 26% to 33%, 18 month (only described in two studies) were 30% and 33% and at 24 months CD4% ranged from 30% to 36%. Kay et al (2012) reported on the average increase in CD4% in two groups according to attainment of virological suppression (21) and Kabue et al (2012) reported on the proportion of infants in whom an increase in over 5% of CD4cells was seen for infants under six months and infants six-12 months (27). McNairy et al (2013) used the variable “illness severity” as a baseline measure to describe those with immunological or disease stage characteristics of a severe nature (36). No study looked at predictors of immune status outcome in infants. An improvement in CD4 cell from baseline measures was consistent in all studies where described and statistically significant improvements from baseline measures were reported in several studies including Omoni et al (2013) and Tukei et al (2013) (16, 29).

Clinical Outcomes

Disease stage was not used as an outcome measure for infants in any of the studies beyond the incidence of stage four events used by Sauvageot et al (2010) (32). Mubiana-Mbewe et al (2009) looked particularly at the incidence of clinical outcomes including upper and lower respiratory tract infections, mucocutaneous infections, malaria and other infections (24). In this study the incident conditions were classified clinically due to the unavailability of diagnostic equipment. These clinical diagnoses, made by clinical officers (not a nurse or a doctor), were not assessed for validity or reliability. In the Mubiana-Mbewe (2009)/Bolton-Moore (2007) study with outcomes measured at presentation to the primary facility the failure to link the databases of other facilities to that used for the analysis may have resulted in an underreporting of severe events as these would present to tertiary institutions and not be relayed to the database of the primary facility for capturing.

Growth Measures

Five studies provide outcomes pertaining to growth, often only described using graphical illustration from which approximate measures were read(23, 30, 41). Growth recovery (WAZ and HAZ > -2) was assessed as the primary outcome by Feinstein et al (2012) (41). Other studies looked at weight-for-age and height-for-age as descriptive outcomes and consistently used WHO 2006 child growth standards and graphs or anthropometric software based thereon for classification (16, 63). The US centres for disease control and prevention charts were used by Janssen et al (2010) to define baseline growth characteristics as their overall cohort included those over the age of 10 years (64). Two studies reported on proportions with WAZ above and below the threshold of -2 with six month proportions of underweight children

improving from a baseline of 63% to 31% at six months (16). Purchase et al (2012) show an improvement from baseline mean weight-for-age z-score of -2.7 to 0.02 at 18 months (22). The outcome height-for-age was reported in three studies with one providing mean values at regular time intervals and the other providing proportions on either side of the -2 threshold, with children with HAZ <-2 considered to be stunted. Forty-eight percent and 60% of infants were stunted at six months after initiation of ART. Weight-for-height was only described in one study with 13.7% of infants being wasted at six months (16).

Loss to Follow Up

Loss to follow up was poorly reported for infants with only six studies reporting on it. Those studies providing this measure for our population of interest provide cumulative probabilities of being LTFU at six months ranging from 0% at six months in Ekouevi et al (2011) to 6-10% depending on immune suppression group in the KIDS-ART LINC (2008) study. At 12 months this probability ranges from approximately 11% in the KIDS-ART LINC (2008) study to 30% in McNairy et al (2013)(36, 39). In the study by McNairy et al (2013) these probabilities of LTFU are further reported as per year of initiation of ART with 12 month probabilities of LTFU decreasing from 35% in 2005 to 27% in 2009 and 24 month probabilities from 39% in 2005 to 37% in 2009.

Janssen et al (2010) is the only study to provide infant LTFU rates and, as seen in mortality outcomes, suggest a high risk period for LTFU in the first 90 days after initiation of ART. This trend can also be seen in the Anaky et al (2010) study as it provides simple proportions of LTFU within the first three months of ART and then in the following nine months with a reduction to over half the proportion of infants

lost to follow up in this second period of nine months than the first three months of ART.

These observed differences in LTFU across the different studies may be due to several different reasons. For example in the Tukei et al (2013) study a small value of a 2% proportion of infants lost to follow up at six months is attributed by the authors in part to their strict inclusion criteria, likely to have been imposed for purposes of minimising LTFU itself, such as stability and presence of caregivers, proximity to the facility and willingness to participate in regular tracing and home visits. There exists significant variation in the prevention, reporting, definition and management of LTFU. This reflects different observation periods, retrospective and prospective cohort designs, effort and ability to ascertain vital status and statistical management in analysis. Of the six studies discussing LTFU only three discussed efforts made to trace these participants with phone calls and home visits in 2 (20, 40) and the other stating no ascertainment of vital status (28). Only four further studies, which did not include LTFU as a reported infant outcome, discuss efforts made to elicit vital status and these efforts range from no tracing effort at all (31) to the use of a full time dedicated on site defaulter tracer with phone and home visits (30).

The definitions of LTFU in general ranged from a loss of contact for 30 days to that of six months. The effect of use of different definitions of LTFU on the estimation of LTFU in ART cohort analysis has been described by Grimsrud et al (2013) as they highlight the need to use consistent definitions when comparing this outcome (1).

The analytic management of LTFU ranged from simple acknowledgement of underestimation of death, complete exclusion from analysis, sensitivity analysis and the alternative measurement of loss to program. No study used a competing risk

analysis for the outcomes of death and LTFU. Overall the Feinstein et al (2012) study of growth outcomes provided the most transparency providing detailed description of LTFU within different subgroups, the assessment of correlation between all covariates with death and LTFU and use of sensitivity analysis to assess selection bias due to LTFU or death. This analysis suggested that only extreme correlation assumptions would affect the null associations observed in the study (41). In comparison Purchase et al (2012) excluded from their study all infants lost to program prior to six months of ART resulting in a population of survivors and non-defaulters – a probable source of selection bias (22). Bias resulting from the association between LTFU and underreported mortality is of particular concern in infants due to their vulnerabilities, correlation of LTFU with other factors associated with poor outcome and the risk of death upon defaulting medication administration (18, 65). Maximisation of efforts to ascertain outcomes is therefore important in preventing this bias.

Loss to Program

Seven studies looked at an outcome which included LTFU (or defaulting care as described by Fetzer et al (2009)) and death together as a measure of retention in care or program attrition. For example, Fetzer et al (2009), for example, a study with no community tracing of defaulters, report a 49% loss to program - a very high proportion when we consider the short overall cohort median follow up time. Purchase et al (2012) measured “completion of ART” at six, 12 and 18 months and reported the predictors thereof (22).

These outcomes as described in these seven studies can be seen summarised below.

Table 4. Loss to Program Outcomes

Author	3 months	6 months	12 months	18 months	24 months	Overall
Fetzer et al (2009) (31)						49% in a median of 196 days follow up
Purchase et al (2012) (22)		27%	**44%**	**59%**		
Tukei et al (2012) (16)		**7%**				
Anaky et al (2012) (20)	20%	**28%**	30%	**34%**		
Sauvageot et al (2010) (32)			32%		43%	
Ekouevi et al (2011) (28)		8.9%	**29.8%**			
McNairy et al (2013) (36)			39%		**49%**	

Other

Other outcomes described for infants were development of BCG Immune reconstitution inflammatory syndrome (IRIS) during ART, hospital admissions during ART, haemoglobin response, albumin response, drug toxicities or adverse events and regimen changes during ART. Drug related outcomes such as adverse events, toxicities and regimen change were rarely described for the infant group largely due to very small numbers. Tukei et al (2013) for example describes 8.3% (N=7) of infants as experiencing adverse treatment events within first six months on therapy. This study also described how by 24 months 44 of the 47 participants who were still in active care were still on first line treatment. They also state that seven children initiated on ART as infants were switched to second line treatment due to persistent viraemia. Kay et al (2012) in comparison, a study also having access to

virological measures, observed 12% of infants experiencing regimen change but all were due to toxicities as the clinical and immunological criteria which were used in the study to direct regimen change, were not met by any of these infants. Sauvageot et al (2010) focusses specifically on toxicity to different drugs and describe a rate of 3.8 events per 100 child years for zidovudine and none for nevirapine or stavudine.

Mubiana-Mbewe et al (2009) describe incident clinical conditions and report a high incidence of 68.5 cases of upper respiratory tract infections (URTI) in infants per 100 child years of observation on ART. Sauvageot et al (2010) also described the outcome of new stage four events and in doing so again highlighted the high risk period of the first three months after initiation of ART with 10.9 events occurring per child year in this period. Purchase et al (2012) describe the change in proportion of infants having experienced hospitalisation for any cause in the last six months at six month intervals of observation. They compare these values to the 74.5% of infants at initiation who had been hospitalised at least once prior to initiation since birth.

Table 5a. Outcomes described – Analytic Infant Outcomes

Author	Follow up Time	Mortality	Virological	Immunological (CD4%)	Growth	LTFU	Other
Bolton–Moore et al (2007) (23)	NRI. Overall: 378 days[a] (138 – 692[c])	Total: 21.1/100 CY[e] (15.4-28.2[CI]) <90d: 52.2/100 CY[e] (35.2-74.5[CI]) >90d: 7.3/100 CY[e] (4.1-12.0[CI])		*(reported graphically)* 6m ±27%[a] 12m ±30%[a] 24m ±35%[a]	**WAZ** *(graphically)* 6m&12m: ±-1.25[b] 18-24m >-1[b]	NRI. *Overall 13%*	**Hb** *(reported graphically)* 12m ±11g/dl[b] 24m ± 12g/dl[b]
Mubiana – Mbewe et al (2009) (24)	NRI. 280 days[a] (110 – 459[c])					NRI *Overall 13.6/100 CY[e]*	**Incident clinical conditions** URTI 68.5/100 CY[e] (48.3-94.5[CI]) LRTI 24.9/100 CY[e] (14.2- 40.4[CI]) Mucocutaneous:56.5/100CY[e](38.3-80.0[CI]) GIT: 53.3/100 CY[e] (36.2-75.8[CI])
Purchase et al (2012) (22)	NR. Observation up to 18 months post-initiation		6m 1.4[a] *log10 copies/ml*, 52%, LDL , 75% < 400 12m 1.4[a] *log10 copies/ml*, 57% LDL , 78% < 400 18m 1.4[a] *log10 copies/ml*, 79% UDL	6m 22.7%[a] (4.7-66.9[d]) 12m 30.6%[a] (7.5-48.7[d]) 18m 33%[a] (9.7-46[d])	**WAZ** 6m -0.51[b] ±1.39[f] 12m -0.05[b] ±1.25[f] 18m - 0.02[b] ± 1.10[f]	NR	**Lost to Program** 6m 27%, 12m 44% 18m 59% **Hb** 6m 11.6g/dl[a] **Hospitalisations:** 6m24.5%, 12m12.9%, 18m2.6% **Regimen change:** 3% **BCG Adenitis <6m**13.8%
Feinstein et al (2012) (41)	NR. Administrative end 2 years				*(graphically)* **WAZ** (%>-2) 6m ±40%, 12m ±90% 18m ±95% **HAZ (%> -2)** 6m ±40%, 12m ±55% 18m ±70%	NRI. *Overall 12%*	
Kay et al (2012) (21)	NR. Observation up to 18 months post-initiation		**Cum. Prob. VS*** 6m 45%, 12m 58% 18m 58% **Time to VS** 3.7m[a] (0.9–8.0[d])	*CD4% increase* **Those with VS*:** 18m: 22%[a] (12-38[d]) **Those without VS*:** 18m: 18%[a] (-3 to 33[d])		NR *Data suggests no LTFU*	**Regimen Change**: 12% (toxicity)
Tukei et al (2013) (16)	752 days[a] (531-980[c])	4.09/100 CY[e] (1.95-8.58[CI])	**Cum. Prob. VS*** 6m 72% (61.6-81.3[CI]) 12m 83% (73.8-90.5[CI]) 24m 84.1%	6m 30%[b] 12m 33%[b] 24m 36%[b]	**WAZ < -2:** 6m 30.8% **HAZ < -2:** 6m 48% **WHZ<-2:** 6m 13.7%	6m 2%	**Adverse events** 6m: 8.3% **Active care**: 6m 93%

*VS =virological suppression as determined by HIV-1 RNA<400 copies ml

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available, CY: Child years, LDL: lower than detectable limit, LTFU: Loss to Follow-up, ART: Antiretroviral Therapy, WAZ: Weight-for-age z score, HAZ: Height-for-age z score, BCG: Bacillus Calmette–Guérin, URTI: Upper Respiratory Tract Infection, LRTI: Lower Respiratory Tract Infection, GIT: Gastrointestinal Urinary, Hb: Haemoglobin
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: month, d: day (Time reference points refer to time since initiation ART)

Table 5b. Outcomes described- Descriptive infant outcomes

Author	Follow-up Time	Mortality (Cumulative Probabilities)	Virological	Immunological (CD4)	Loss to Follow Up (Cumulative Probabilities)	Other
Bong et al (2007) (33)	NR. (up to 6 months post-initiation)	3m: 18.9% 6m: 24.3%			NRI *Overall cohort 9%*	
KIDS-ART LINC (2008) (39)	NRI. Overall: 20.3 months[a] (11.7-27.9[c])	*(reported graphically)* 6m ± 15% 12m, 18m, 24m: ± 17.5%			*(reported graphically)* 6m: ± 6% - 10%, 12m: ± 11 % 18m: 14%, 24m: 14%- 20%	
Fetzer et al (2009) (31)	NRI. Overall: 196 days[a] (105-310[c])				NR	**Loss to program:** 49%
Davies et al (2009) (25)	NRI. Overall 16 months[a] (6-29[c])	*(reported graphically)* 6m ± 13%, 12m ±15% 18m ± 16%, 24m ± 16% 36m ± 17%			NRI *Overall cohort 12m:2.2%in those initiating prior to 2004 and 8.2% in those initiating 2006 or later*	**Transfer Out:** Overall 24m: 50% of tertiary cohort
Anaky et al (2010) (20)	NR	6m: 0.14 (0.07-0.21[CI]) 12m: 0.16 (0.10-0.22[CI]) 18m: 0.16 (0.10-0.22[CI]) **Mortality Rates** Total: 20.9/100 CY[e] (11.3-30.5[CI]) 0-3m: 43.7/100 CY[e] (19.5-69.0[CI]) 4-12m: 9.8/100 CY[e] (1.8-17.8[CI])			**Proportions** Total:15% 0-3 months:11%, 4-12m: 5.5%	**Loss to Program** 3m: 0.20 (0.13-0.27[CI]) 6m: 0.28 (0.20-0.36[CI]) 12m: 0.30 (0.21-0.39[CI]) 18m: 0.34 (0.25-0.43[CI])
Janssen et al (2010) (40)	NR. 732 child-years	**Mortality Rates** Total: 76.2/1000 CY[e] (61.3- 94.3[CI]) <90d:149/1000 CY[e] (128.3-173.4[CI]) >90d: 61.3/1000 CY[e] (48.0-77.9[CI])	12m: 4.7[a] *log$_{10}$ copies/ml* (3.4-6.2[c]) *(64% missing)*	12m: 26%[a] (20-30[c]), 1077[a] cells/µl (712-1343[c]) *(50% missing)*	**LTFU Rates** Total: 50.8/1000 CY[e] (38.8-66.2[CI]) < 90d: 74.5/1000 CY[e] (59.8 -92.5[CI]) >90d: 46.0/1000 CY[e] (34.6-60.7 [CI])	**Albumin:** 12m: 35[a] (30-36[c]) *(75% missing)* **Transfer Out:** 2.5% **Hb:**12m: 10.7[a] (10.5-11.2[c]) *(97.6% missing)*
Fenner et al (2010) (26)	NRI. Overall: 17.3 months[a] (8.7-25.7[d])	12m: 15.3/100 CY[e]			NRI *Overall:12m: 7%*	**Transfer out** *Overall: 14.3%*

*VS =virological suppression as determined by HIV-1 RNA<400 copies ml ** Viral Rebound: > 1000 copies/ml after suppression

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available, CY: Child years, LTFU: Loss to Follow-up, Hb: Haemoglobin
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months, d: day (Time reference points refer to time since initiation ART)

Table 5b. Outcomes described- Descriptive infant outcomes continued

Author	Follow-up	Mortality (Cumulative Probabilities)	Virological	Immunological (CD4)	Loss to Follow Up (Cumulative Probabilities)	Other
Sauvageot et al (2010) (32)	NRI. Overall 10.5 months[a] (3.7-20.6 [c])	**Survival** 12m: 0.85 (0.79-0.89[CI]) 24m: 0.80 (0.71- 0.86[CI])			NR	**Remaining in care** 12m: 0.68 (0.60-0.74[CI]), 24m: 0.57 (0.47-0.65[CI]) **Stage 4 Events**0-6m: 10.9 events/ CY[e] (5.3-20.3[CI]), 6-12m: 6.3/CY[e] (2.0-19.5[CI]), >12m: 4.7/ CY[e] (1.2-18.3[CI]) **Toxicities:** 6m: No events for NVP or D4T. AZT: 3.8 events/100 CY[e] (0.9-15.1[CI])
Meyers et al (2011) (30)	12.3 months[a] (3.6-24.8 [c])	**Mortality Rates** Total: 10.7/100 CY[e] (8.4-13.7[CI]) <90d: 32.08/100 CY[e] (23.6-45.7[CI]) >90d: 5.9/100 CY[e] (4.1-8.5 [CI])	**Proportion attaining: VS[*]:** 84.5% **Viral Rebound[**]** 9.36%	*(reported graphically)* 6m: ± 23%[a] 12m: ± 26.5%[a] 18,24 & 36m: ±30%[a]	NRI *Overall Cohort: 6%*	**HAZ** *(reported graphically)* 6m: ± 2.75[b], 12m: ± -2.5[b] 18m: ± -2.4[b], 24m: ± -2.2[b]
Ekouevi et al (2011) (28)	NRI. Overall: 1761 child-years.	6m: 8.9% (3.4-22.2[CI]) 12m: 10.7% (5.0-26.0[CI])			6m: 0.00 (0.00-0.00 [CI]) 12m: 20.2 (10.2;37.8 [CI])	**Loss to Program** 6m: 8.9% (3.4-22.2[CI]) 12m: 29.8% (18.0-46.6[CI])
Kabue et al (2012) (27)	NRI. Overall: 2.3 years[a] (1.5–3.1 [c])	**Proportion Deaths** **Age < 6m:** 12m: 15.1% **Age 6–12m:** 12m: 5.7%		**% with >5% increase in CD4%** **Age< 6 m:** 12m: 78.8% **Age 6-12m:** 12m: 85.5%	NRI *Overall Cohort: 9%*	
McNairy et al (2013) (36)	NRI. Overall: 598 days[a] (245-1106[c])	**Total:**12m: 13%, 24m: 18% **2005**:6m: 11%, 24m: 21% **2009** 6m: 12%, 24m: 16%			**Total:**12m: 30%, 24m: 39% **2005**: 12m: 35%, 24m: 39% **2009**: 12m: 27%, 24m: 37%	**Retention in care:** **Total:**12m: 61%, 24m: 51% **2005:**12m: 57%, 24m: 48% **2009:**12m: 64%, 24m: 53%
Omoni et al (2013) (29)	NR. Up to 12 months post-initiation			12m: 28.9%[b] (24.4-33.4[d])	NRI *Overall Cohort: 7.3%*	

*VS =virological suppression as determined by HIV-1 RNA<400 copies ml ** Viral Rebound: > 1000 copies/ml after suppression

NR: Not reported, NRI: Not reported for infants, overall cohort statistics provided where available, CY: Child years, UDL: Undetectable limit, HAZ: Height-for-age z score
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months, d: day (Time reference points refer to time since initiation ART)

Determinants of infant outcomes

Within those studies reporting results on the predictors of the primary outcome in infants the predictors assessed were largely immunological, virological, clinical, growth and regimen baseline characteristics. In addition serum creatinine and adherence were assessed as determinants for mortality (24). The results of these analyses are presented in **Table 6** below.

Of the six studies providing an analysis of predictors of outcomes specifically for the infant subgroup, three did not yield significant results. Predictors were identified for mortality and for virological suppression at 18 months. Further analysis of univariate association between loss to program at 18 months suggests that mean CD4 cell count differs significantly in those that do and do not remain alive and in care to this point (22). In a multivariate Cox proportional hazards regression analysis identifying predictors of time to death in 291 infants age below 18 months with a median age of six months at ART initiation identified lower categories of weight-for-age and CD4 cell percentage as being associated with death. The sample on which this analysis was done was 157 completed cases. Adjustment for all variables found in the univariate analysis to be associated with death at $p<0.1$ as well as all variables found to be significant in the adult and older child cohorts of the overall study. The estimates are very large (Hazard ratio (HR) of 19 for an infant with WAZ $\leq$-3 compared to >-1 when all other variables are kept constant) but despite non-inclusion of the null value have very wide confidence estimates (2.4-150 for this estimate). This suggests that the data may have been too few or too varied to attain a precise estimate and that uncertainty as to the validity of this estimate exists.

Predictors for time to virological suppression were identified in the Kay et al (2012) study. These included age in months, viral load and CD4 cell percentage at initiation of ART. Again the wide confidence intervals reflect the small sample size - in this case 34 infants.

Tukei et al (2013) provide a logistic regression analysis of factors associated with attainment of virological suppression at six months. This analysis was however restricted to those infants remaining on ART for at least six months. As reported in the studies by Anaky et al (2010) and Bolton-Moore et al (2007) we know that this early period is a time of extreme risk of death. Exclusion of those infants not surviving this period would result in a population with characteristics different to the general population initiating ART and excluded a significant portion of infants in who the association might have been observed. Additionally it could possibly have aggravated an already existing survival bias. Furthermore the use of logistic regression where informative censoring has not been considered may have resulted in biased estimates.

The classification of the outcome incident clinical conditions into several groups in the Mubiana-Mbewe et al (2009) study may have resulted in the infant population of 101 participants being further divided into very small subgroups and may have contributed to the failure to ascertain a significant association.

Table 6. Determinants of infant outcomes

Author	Primary Outcomes	Baseline Predictors assessed	Baseline Predictors identified			Comments
Bolton–Moore et al (2007) (23)	Mortality	Age (months), CD4 %, WAZ, Hb, sex, TB, creatinine WHO stage, regimen, adherence,	**WAZ scores**	**Crude**	**Adjusted**	Cox regression. Adjusted for all factors found in univariate analysis to be significant the p <0.10 level as well as those found significant in the adult study.
			WAZ >-1	Reference	Reference	
			WAZ >-2 to -1	HR 1.9 (0.3-11.5 CI)	HR 4.7(0.5-45.9 CI)	
			WAZ >-3 to -2	HR 6.1 (1.3-27.7 CI)	HR 17 (2.0-141 CI)	
			WAZ ≤-3	HR 9.7 (2.3-40.9 CI)	HR 19 (2.4-150 CI)	
			CD4 cell percentage			
			CD4 ≥20%:	Reference	Reference	
			CD4 10 to <20%:	HR 4.7 (1.4-15.7 CI)	HR 16 (2.1-123 CI)	
			CD4 < 10%:	HR 5.2(1.4-18.8 CI)	HR 18 (2.1-151 CI)	
Mubiana – Mbewe et al (2009) (24)	Incident clinical conditions	CD4 %, gender, WAZ, WHO stage, Hb.	**None**	*Only univariate analysis done for infant subgroup, no significant associations identified.*		
Purchase et al (2012) (22)	Loss to Program at 18 months	Age, gender, NVP exposure, WHO stage, TB, CD4%, VL	**CD4 cell percentage** Those completing 18 months: vs Those not completing 18 months:	Mean CD4 cell%: 14% Mean CD4 cell%: 17.7% (p=0.005)	Analysis was only done on those who completed 6 months of treatment	
Feinstein et al (2012) (41)	Weight recovery (WAZ > -2) Height recovery (HAZ > -2)	Baseline CD4	**None**	*Severe immunodeficiency (CD4%<25%) not found to be associated with weight recovery (adjusted HR 1.17 (95%CI 0.69-1.99)) nor height recovery (adjusted HR 1.02 (95%CI 0.56-1.88))*		
Kay et al (2012) (21)	Virological suppression*	CD4, VL, gender, WHO stage, breastfeeding	**Age**	**Crude**	**Adjusted**	Cox Proportional Hazards Regression
			per 1 month increase	HR 1.29 (1.14-1.47 CI)	HR 1.28 (1.10-1.49 CI)	
			Viral Load			
			< 750 000 copies/ml	HR 4.95 (1.74-14.1 CI)	HR 3.54 (1.13-11.1 CI)	
			CD4 cell percentage			
			>25%	HR 5.00 (1.75-14.3 CI)	HR 6.0 (1.83-19.6 CI)	
Tukei et al (2013) (16)	Virological suppression* at 6 months	Gender, CD4 %, WHO stage, WAZ, HAZ, WHO guidelines, regimen	**None**	*Analysis was only done on those who completed 6 months of treatment Logistic regression*		

*Virological suppression as determined by HIV-1 RNA<400 copies ml

ART: Antiretroviral Therapy, WAZ: Weight-for-age z score, HAZ: Height-for-age z score, Hb: Haemoglobin, TB: Tuberculosis, WHO: World Health Organisation, NVP: Nevirapine, VL: Viral load
a: median, b: mean, c: Interquartile Range, d: Range, e: rate per no. child years, f: Standard Deviation, CI: 95% Confidence Interval, m: months, HR: Hazard Ratio

Summary, Interpretation and needs for further research

The findings of the studies in this review can be summarised in accordance with the respective objectives of the review.

1. ***To identify all published literature pertaining to studies assessing the outcomes (and where available the predictors of these outcomes) of infants initiated on ART in routine care in Sub-Saharan Africa,***

Using an electronic database and a keyword search 998 published articles were identified, 18 of which satisfied the inclusion and non-exclusion criteria. A further article (20), meeting the same inclusion criteria, was identified through examining bibliographies of reviews and articles identified. In keeping with the inclusion criteria all reported on outcomes specifically pertaining to an infant group and 6 of these provided results from the analysis of predictors for these outcomes.

2. ***To consider the evidence provided by the literature regarding all 3 objectives of the mini-dissertation, and to review and report on the quality and results of the studies by critically reading and synthesising the findings and evidence regarding the outcomes of these infants,***

   Objective 1: To describe the baseline characteristics of infants commencing ART in IeDEA sites in Southern Africa.

Baseline characteristics for an infant group or subgroup were not very well reported in the majority of studies. Clinical disease severity (by means of WHO staging) and immunological measures (CD4 counts, percentages and prevalence of percentage categories) were the most consistently measured and reported measures yet both commonly yielded high levels of missing data. PMTCT and cotrimoxazole exposure

were the most poorly recorded and reported variables commonly not measured or measured with high levels of missing data.

When considering clinical, immunological, virological and growth measures together, as in keeping with the aim of the mini dissertation which this review aims to inform, we can identify a few trends amongst the studies with which we can identify those studies wherein infants starting ART are either relatively healthy or unwell.

Kay et al (2012) represent a population of infants at a relatively young age with some of the most favourable WHO staging, highest CD4 measures, lowest viral loads and relatively good weight-for-age measures. They however represent a population where PIs were not available and all used a non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen (nevirapine) despite all being nevirapine- exposed through PMTCT. Similarly Janssen et al (2010) represents a population with favourable immunological, virological and growth measures but differ in the older age, a moderate WHO staging and very high tuberculosis prevalence compared to the other studies providing results of these measures in infants.

In contrast when we look at the study by Meyers et al (2011), observing a relatively young population of infants, the measures of these baseline characteristics are amongst the worst regarding clinical disease, CD4 count and percentage, viral load and weight and height-for-age. Furthermore this group has one of the highest prevalence of tuberculosis at initiation making them a significantly unwell population of infants in whom we would expect poor outcomes.

When briefly compared to those characteristics of infants initiating ART in trials in the same region of Sub-Saharan Africa we note that the infants in the majority of the

observational studies in this review were much older and had higher prevalence of characteristics indicating more severe disease severity. Most notably we see this in immunological characteristics largely due to the inclusion criteria e.g CHER (Violari et al (2008)) excluding all infants with CD4%<25% (4). Furthermore in observational studies conducted in the developed world these characteristics, particularly immunological, were at far better levels than any of the studies in this review (5).

Objective 2: To describe and examine the outcomes of infants starting ART in Southern Africa. Summary of Outcomes

These observational studies show that infants initiated on ART improved regarding all immunological, virological and growth measures as well as frequency of hospitalisations and haemoglobin. This provides supporting evidence to the fact that ART is effective in infants beyond the trial setting.

The magnitude of these improvements and the occurrence of outcomes of death, loss to follow up and virological suppression outcomes differed considerably in the different studies. Variation appears to reflect in part the distribution of baseline characteristics (particularly age at initiation and disease severity) and on definition or methods of ascertainment of the outcomes, particularly loss to follow up, as reflected in the sections above. Furthermore programmatic factors such as year of observation, prevailing ART initiation guidelines and availability of ART regimens may be responsible for a component of the observed differences. Study characteristics of length of follow up also appear to considerably affect the estimates due to the non-constant nature of risk of these infant outcomes through time. Where baseline characteristics reflect those of the chronological, geographical and

programmatic situation this information provides us with an understanding of the impact of these factors on the cohort profile. Where these characteristics are a result of selection process, however, we hold concern as to the validity of these findings and specifically to the external validity – its generalizability to our study population.

Objective 3: To identify and examine predictors for these outcomes.

Of note is the scarcity of evidence pertaining to the predictors of outcomes of infants. Only six studies did such an analysis, only two of which used multivariate statistical methods appropriate to the longitudinal nature of the data. The neglect of the issue of censoring as done in the other analyses could result in a biased estimate.

Sample size was of concern in almost all of these analytic studies. Whether a result of available participants, categorisation of outcomes or exclusion the resulting sample sizes have, even where estimates appear considerable, failed to provide certainty.

Summary of study quality and validity

Due to the specific inclusion criteria with its chronological, geographical, age and routine setting characteristics there was, in general, homogeneity in the populations in the articles used in this review. There is variation in the age group however as a paucity of literature led to the inclusion of infants up to 19.9 months of age. Sample size differs significantly when assessing the infant population with smaller sizes being seen in those articles best pertaining to our research objectives with the reporting of predictors of outcomes for infants. Median follow up rarely exceeded two years and was often not reported for the infant subgroup.

The main issues of validity which we have discussed in the previous sections are those of selection bias. This includes several issues including survival bias, management of missing data (as exclusion in complete case analysis is itself selection), LTFU and study exclusion criteria. These biases, all common in cohort data, are possibly emphasized in the infant population due to their rapidly changing physiology and physical and social vulnerabilities resulting not only in a wide range of disease characteristics but also risk of outcomes, particularly death and loss to follow up (10, 66).

No cohort is thus truly comparable to another and differences in baseline characteristics, programmatic factors and their outcomes are inevitable. This however, does not necessarily represent invalidity but rather, highlights for us the extreme effects of changing guidelines and infant ART programs, resource provision and in doing so provides us with a valid description of infants who are initiating ART in Southern Africa.

The ideal study for purposes of fulfilling the objectives of this review would have included a sample of infants < 12 months of age which met calculated sample size calculations to ascertain the strength of associations in its outcomes and predictors thereof. Participants should represent the population which routinely accesses standard care in these resource scarce settings and restriction of inclusion discouraged as it deters from our aim of assessing routine setting outcomes and rather approximates the populations seen in experimental studies. Focus would be on the outcomes of these infants and in so doing allowing for measure of multiple outcomes and assessing for the predictors thereof. The observation period should have been as long as plausible so as to maximise the opportunity for observing both short and long term outcomes particularly in view of the prospect of life-long

treatment which these infants have. It would ensure the accurate ascertainment of loss to follow up with as much effort as feasible while at the same time not limiting inclusion to the extent of decreasing generalizability. Furthermore ascertainment of vital status should be done as far as possible and analytic consideration of the effect of false assumptions through sensitivity analysis done. It would have logically, based upon existing literature, assessed the role of possible confounders and other third variables and correctly managed these. In a similar way transparency for occurrence and management of sources of bias such as loss to follow up, censoring and missing data should have been provided.

None of the studies reviewed here fulfil all these criteria. Although providing methodologically strong evidence the Feinstein et al (2012) study does not adequately apply to our research questions. Tukei et al (2013) and Bolton-Moore et al (2007) address the aim of our study most directly however issues of sample size and generalizability for Tukei et al (2013) and management of confounders and prevention of bias are of concern in the Bolton-Moore et al (2007) study. Despite some shortcomings, together these studies provide valuable insight into the expression of associations for a range of outcomes and predictors in a resource poor setting of sub-Saharan Africa, highlight possible methodological and statistical pitfalls and establish a foundation and background upon which the findings of the study of this mini-dissertation may be placed.

3. ***To synthesise this information and to identify areas where further research would be gainful.***

The Drugs for Neglected Disease initiative declared Paediatric HIV as one of the globally neglected diseases in 2010 (14). This review highlights that amongst this

group stands an even more severely neglected population – HIV infected infants. With a severe paucity of evidence, particularly in the lower to middle income countries within Southern Africa where the majority of these infants live and die (66, 67), there exists a large gap in the knowledge of the characteristics and outcomes of HIV infected infants initiating ART.

To attain a generalizable description of baseline characteristics and outcomes with certainty in its analysis for predictors for these outcomes we require recent evidence from a large sample of multiple cohorts from varied routine settings.

IeDEA is an international initiative formed by the pooling of several large data sets each comprised of HIV infected individuals attending standard care at participating sites (1, 68, 69). The collaboration of IeDEA- SA involves sites from South Africa, Zimbabwe, Mozambique, Malawi, Botswana and Zambia all of which have HIV adult prevalence rates above 10% (10, 70). The main objectives of IeDEA-SA are "to conduct clinical, epidemiological and health services research in order to inform HIV/AIDS and tuberculosis service delivery in the region, to increase the capacity for delivering ART, and, ultimately, to improve the prognosis of people living with HIV and AIDS in Southern Africa." (70) The IeDEA-SA database is constituted of data routinely recorded from participants at every clinic visit and collected on site by site investigators using a Data Transfer Protocol **(Appendix A).** This Data includes baseline and follow up visit data using standardised definitions as per the protocol.

This data therefore offers us the opportunity to address the research objectives. It will help us address the research questions of "What are the outcomes of infants starting ART in routine care in Southern Africa?" and "What are the predictors of these outcomes?"

References

1. Grimsrud AT, Cornell M, Egger M, Boulle A, Myer L. Impact of definitions of loss to follow-up (LTFU) in antiretroviral therapy program evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU. Journal of Clinical Epidemiology. 2013 Jun 14.

2. Hoskins S, Weller I, Jahn A, Kaleebu P, Malyuta R, Kirungi W, et al. An appraisal of indicators used to monitor the treated population in antiretroviral programmes in low-income countries. Official Journal of the International AIDS Society. 2010 Nov 13;24(17):2603-7.

3. World Health Organisation. Report of the WHO Technical Reference Group: WHO Antiretroviral Therapy for Infants and Children 2008 ,2008: Available from: http://www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf.

4. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. New England Journal of Medicine. 2008;359(21):2233-44.

5. Faye A, Le Chenadec J, Dollfus C, Thuret I, Douard D, Firtion G, et al. Early versus deferred antiretroviral multidrug therapy in infants infected with HIV type 1. Clin Infect Dis. 2004 Dec 1;39(11):1692-8.

6. Berk DR, Falkovitz-Halpern MS, Hill DW, Albin C, Arrieta A, Bork J, et al. Temporal Trends in Early Clinical Manifestations of Perinatal HIV Infection in a Population-Based Cohort. Journal of the American Medical Association. 2005;293(18):2221-31.

7. Chiappini E, Galli L, Tovo P-A, Gabiano C, Gattinara GC, Guarino A, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. Official Journal of the International AIDS Society. 2006;20(2):207-15.

8. McGrath CJ, Chung MH, Richardson BA, Benki-Nugent S, Warui D, John-Stewart GC. Younger age at HAART initiation is associated with more rapid growth reconstitution. Official Journal of the International AIDS Society. [Research Support, N.I.H., Extramural

Research Support, U.S. Gov't, P.H.S.]. 2011 Jan 28;25(3):345-55.

9. Prendergast AJ, Penazzato, M., Cotton, M., Musoke, P., Mulenga, V., Abrams, E.J., Gibb, D.M.,. Treatment of Young Children with HIV Infection: Using Evidence to Inform Policymakers. PLoS Med 2012;9(7):e1001273.

10. UNICEF. HIV and AIDS. Eastern and Southern Africa. . 2013 [updated 2012; cited 2013 14 October]; Available from: http://www.unicef.org/esaro/5482_HIV_AIDS.html.

11. Spira R, Lepage P, Msellati P, Van de Perre P, Leroy V, Simonon A, et al. Natural History of Human Immunodefiency Virus Type 1 Infection in Children: A Five-Year Prospective Study in Rwanda. Pediatrics 1999;104(e56).

12. Braun M, Kabue MM, McCollum ED, Ahmed S, Kim M, Aertker L, et al. Malawi inadeqate coord maternal & infant HIV services detrimentally affects early infant diag outcomes. Journal of Acquired Immune Deficiency Syndrome. 2011;56:122-8.

13. Lallemant M, Chang S, Cohen R, Pecoul B. Pediatric HIV — A Neglected Disease? New England Journal of Medicine. 2011;365(7):581-3.

14. DNDi. Drugs for Neglected Diseases Initiative. 2013 [cited 2013 14/06/2013]; Available from: http://www.dndi.org/diseases-projects/diseases/paediatric-hiv.html.

15. Prendergast A, Mphatswe W, Tudor-Williams G, Rakgotho M, Pillay V, Thobakgale C, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. Official Journal of the International AIDS Society. 2008 Jul 11;22(11):1333-43.

16. Tukei VJ, Murungi M, Asiimwe AR, Migisha D, Maganda A, Bakeera-Kitaka S, et al. Virologic, immunologic and clinical response of infants to antireteroviral therapy in Kampala, Uganda. BMC Pediatrics. 2013;13(42).

17. Hsiao NY, Stinson K, Myer L. Linkage of HIV-infected infants from diagnosis to antiretroviral therapy services across the Western Cape, South Africa. PLoS ONE. 2013;8(2):e55308.

18. Leroy V, Malateste K, Rabie H, Lumbiganon P, Ayaya S, Dicko, F., Davies M-A, et al. Outcomes of Antiretroviral Therapy in Children in Asia and Africa: A Comparative Analysis of the IeDEA Pediatric Multiregional Collaboration. Journal of Aquired Immune Deficiency Syndrome. 2013(62):208-19.

19. National Library of Medicine US, National Institute of Health US. PubMed. 1993 ed. Bethesda2013.

20. Anaky MF, Duvignac J, Wemin L, Kouakoussui A, Karcher S, Toure S, et al. Scaling up antiretroviral therapy for HIV-infected children in Cote d'Ivoire:

determinants of survival and loss to programme. Bulletin: World Health Organisation. 2010 Jul 1;88(7):490-9.

21. Kay J, Wanzira H, Sandison T, Kakuru A, Bigira V, Kamya M, et al. Virologic suppression in nevirapine-exposed HIV-infected infants initiating antiretroviral therapy in rural Uganda. Journal of Tropical Pediatrics. 2012 Jun;58(3):194-9.

22. Purchase SE, Van der Linden DJ, McKerrow NH. Feasibility and effectiveness of early initiation of combination antiretroviral therapy in HIV-infected infants in a government clinic of Kwazulu-Natal, South Africa. J Trop Pediatr. 2012 Apr;58(2):114-9.

23. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, Chintu N, Stringer EM, Chi BH, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. Journal of the American Medical Association. 2007 Oct 24;298(16):1888-99.

24. Mubiana-Mbewe M, Bolton-Moore C, Banda Y, Chintu N, Nalubamba-Phiri M, Giganti M, et al. Causes of morbidity among HIV-infected children on antiretroviral therapy in primary care facilities in Lusaka, Zambia. Trop Med Int Health. 2009 Oct;14(10):1190-8.

25. Davies M-A, Keiser O, Technau K, Eley B, Rabie H, van Cutsem G, et al. Outcomes of the South African National Antiretroviral Treatment Programme for children: The IeDEA Southern Africa collaboration. South African Medical Journal. 2009(99):730-7.

26. Fenner L, Brinkhof MW, Keiser O, Weigel R, Cornell M, Moultrie H, et al. Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa. Journal of Acquired Immune Deficiency Syndrome. 2010 Aug;54(5):524-32.

27. Kabue MM, Buck WC, Wanless SR, Cox CM, McCollum ED, Caviness AC, et al. Mortality and clinical outcomes in HIV-infected children on antiretroviral therapy in Malawi, Lesotho, and Swaziland. Pediatrics. 2012 Sep;130(3):e591-9.

28. Ekouevi DK, Azondekon A, Dicko F, Malateste K, Toure P, Eboua FT, et al. 12-month mortality and loss-to-program in antiretroviral-treated children: The IeDEA pediatric West African Database to evaluate AIDS (pWADA), 2000-2008. BMC Public Health. 2011;11:519.

29. Omoni AO, Christian PS, Sadoh WE, Okechukwu A, Olateju E, Omoigberale A, et al. Immunologic Outcomes of Antiretroviral Therapy among HIV-Infected Nigerian Children and its Association with Early Infant Feeding and Nutritional Status at Treatment Initiation. Pediatric Infectious Diseases Journal. 2013 Feb 13.

30. Meyers TM, Yotebieng M, Kuhn L, Moultrie H. Antiretroviral therapy responses among children attending a large public clinic in Soweto, South Africa. Pediatric InfectIous Diseases Journal. 2011 Nov;30(11):974-9.

31. Fetzer BC, Hosseinipour MC, Kamthuzi P, Hyde L, Bramson B, Jobarteh K, et al. Predictors for mortality and loss to follow-up among children receiving anti-retroviral therapy in Lilongwe, Malawi. Tropical Medicine & International Health 2009 Aug;14(8):862-9.

32. Sauvageot D, Schaefer M, Olson D, Pujades-Rodriguez M, O'Brien DP. Antiretroviral therapy outcomes in resource-limited settings for HIV-infected children <5 years of age. Pediatrics. 2010;125(5):e1039-47.

33. Bong CN, Yu JK, Chiang HC, Huang WL, Hsieh TC, Schouten EJ, et al. Risk factors for early mortality in children on adult fixed-dose combination antiretroviral treatment in a central hospital in Malawi. Journal of the International AIDS Society. 2007 Aug 20;21(13):1805-10.

34. Ntanda H, Olupot-Olupot P, Mugyenyi E, Kityo C, Lowes R, Cooper C, et al. Orphanhood predicts delayed access to care in Ugandan children The Pediatric Infectious Disease Journal. 2009 Feb;28(2):153-5.

35. Fatti G, Bock P, Grimwood A, Eley B. Increased vulnerability of rural children on antiretroviral therapy attending public health facilities in South Africa: a retrospective cohort study. Official Journal of the International AIDS Society. 2010;13:46.

36. McNairy ML, Lamb MR, Carter RJ, Fayorsey R, Tene G, Mutabazi V, et al. Retention of HIV-infected children on antiretroviral treatment in HIV care and treatment programs in Kenya, Mozambique, Rwanda, and Tanzania. Journal of Acquired Immune Deficiency Syndrome. 2013 Mar 1;62(3):e70-81.

37. World Health Organisation. Antiretroviral Therapy For HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a public health approach. 2010 revision2010: Available from: http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf.

38. Zanoni BC, Phungula T, Zanoni HM, France H, Cook EF, Feeney ME. Predictors of poor CD4 and weight recovery in HIV-infected children initiating ART in South Africa. PLoS ONE. [Research Support, Non-U.S. Gov't]. 2012;7(3):e33611.

39. KIDS ART LINC. Low risk of death, but substantial program attrition, in pediatric HIV treatment cohorts in Sub-Saharan Africa. Journal of Acquired Immune Deficiency Syndrome. 2008 Dec 15;49(5):523-31.

40. Janssen N, Ndirangu J, Newell ML, Bland RM. Successful paediatric HIV treatment in rural primary care in Africa. Archives of Diseases in Childhood. 2010;95(6):414-21.

41. Feinstein L, Yotebieng M, Moultrie H, Meyers T, Van Rie A. Effect of baseline immune suppression on growth recovery in HIV positive South African children receiving antiretroviral treatment. Journal of Acquired Immune Deficiency Syndrome. 2012 Oct 1;61(2):235-42.

42. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Statistics in Medicine. 1999 Mar 30;18(6):681-94.

43. Patrician PA. Multiple imputation for missing data. Research in Nursing and Health. 2002 Feb;25(1):76-84.

44. Marston M, Becquet R, Zaba B, Moulton LH, Gray G, Coovadia H, et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. Int J Epidemiol. [Research Support, Non-U.S. Gov't]. 2011 Apr;40(2):385-96.

45. Bourne DE, Thompson M, Brody LL, Cotton M, Draper B, Laubscher R, et al. Emergence of a peak in early infant mortality due to HIV/AIDS in South Africa. Journal of the International AIDS Society. 2009 Jan 2;23(1):101-6.

46. AIDS Info US, Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection [cited 2014: Available from: http://aidsinfo.nih.gov/guidelines.

47. Berhane R BD, Marum L, Aceng E, Ndugwa C, Bosch RJ, et al. Growth failure as a prognostic indicator of mortality in pediatric HIV infection. . Pediatrics. 1997;100(E7).

48. Shiau S, Arpadi S, Strehlau R, Martens L, Patel F, Coovadia A, et al. Initiation of Antiretroviral Therapy Before 6 Months of Age is Associated with Faster Growth Recovery in South African Children Perinatally Infected with Human Immunodeficiency Virus. J Pediatr. 2013 Jan 10.

49. Anabwani G, Navario P. Nutrition and HIV/AIDS in sub-Saharan Africa: an overview. Nutrition. [Review]. 2005 Jan;21(1):96-9.

50. World Health Organisation. Global HIV/AIDS response: Epidemic update and health sector progress towards Universal Access 2011 Progress Report2011: Available from: http://www.who.int/hiv/pub/progress_report2011/en/.

51. Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lancet. 2004 Nov 20-26;364(9448):1865-71.

52. Mulenga V, Ford D, Walker AS, Mwenya D, Mwansa J, Sinyinza F, et al. Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children. Official Journal of the International AIDS Society. 2007 Jan 2;21(1):77-84.

53. Wiseman CA, Schaaf HS, Cotton MF, Gie RP, Jennings T, Whitelaw A, et al. Bacteriologically confirmed tuberculosis in HIV-infected infants: disease spectrum and survival. Int J Tuberc Lung Dis. [Research Support, N.I.H., Extramural]. 2011 Jun;15(6):770-5.

54. Ballif M, Renner L, Dusingize J, Leroy V, Ayaya S, Wools-Kaloustian K, et al. Tuberculosis in Pediatric Antiretroviral Therapy Programs in Low- and Middle-Income Countries: Diagnosis and Screening Practices. Journal of the Pediatric Infectious Diseases Society. 2014;In Press(DOI:10.1093/jpids/piu020).

55. Palumbo P, Lindsey JC, Hughes MD, Cotton MF, Bobat R, Meyers T, et al. Antiretroviral Treatment for Children with Peripartum Nevirapine Exposure. New England Journal of Medicine. 2010;363(16):1510-20.

56. Violari A, Lindsey JC, Hughes MD, Mujuru HA, Barlow-Mosha LN, Kamthunzi P, et al. Nevirapine versus Ritonavir-Boosted Lopinavir for HIV-Infected Children. New England Journal of Medicine. 2012;366:2380-9.

57. Seidenberg P, Nicholson S, Schaefer M, Semrau K, Bweupe M, Masese N, et al. Early infant diagnosis of HIV infection in Zambia through mobile phone texting of blood test results. Bull World Health Organ. 2012 May 1;90(5):348-56.

58. Chatterjee A, Tripathi S, Gass R, Hamunime N, Panha S, Kiyaga C, et al. Implementing services for Early Infant Diagnosis (EID) of HIV: a comparative

descriptive analysis of national programs in four countries. BMC Public Health. 2011;11:553.

59. Goel MK, Khanna P, Kishore J. Understanding survival analysis: Kaplan-Meier estimate. International Journal of Ayurveda Research. 2010 Oct;1(4):274-8.

60. Weigel R, Estill J, Egger M, Harries AD, Makombe S, Tweya H, et al. Mortality and loss to follow-up in the first year of ART: Malawi national ART programme. Official Journal of the International AIDS Society. 2012 Jan 28;26(3):365-73.

61. Penazzato M, Prendergast A, Tierney J, Cotton M, F. , Gibb D. Effectiveness of antiretroviral therapy in HIV-infected children under 2 years of age (Review). Cochrane Database Systematic Review. 2012.

62. Davies MA, Phiri S, Wood R, Wellington M, Cox V, Bolton-Moore C, et al. Temporal trends in the characteristics of children at antiretroviral therapy initiation in southern Africa: the IeDEA-SA Collaboration. PLoS ONE. 2013;8(12):e81037.

63. World Health Organisation. WHO Child Growth Standards based on length/height, weight and age2006; 450: Available from: www.ncbi.nlm.nih.gov/pubmed/16817681.

64. Centre for disease control. Growth Charts: United States. [cited 2013 11/01]; Available from: http://www.cdc.gov/growthcharts/.

65. Davies M-A. Outcomes and effectiveness of antiretroviral therapy for HIV-infected children in Southern African treatment cohorts. Unpublished thesis presented for the degree of Doctor of Philosophy In the School of Public Health and Family Medicine University of Cape Town. 2013.

66. World Health Organisation. Early detection of HIV infection in infants and children. Guidance note on the selection of technology for the early diagnosis of HIV in infants and children. Summary of recommendations. 2007: Available from: http://www.who.int/hiv/paediatric/EarlydiagnostictestingforHIVVer_Final_May07.pdf.

67. UNICEF. Towards an AIDS-Free Generation 2012: Available from: http://www.unicef.org/aids/files/hiv_InfographicREV2.pdf.

68. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P, et al. Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol. 2012 Oct;41(5):1256-64.

69. IeDEA. The International Epidemiologic Database to Evaluate AIDS Web Page. NIH; [12/07/2013]; Available from: http://www.iedea.org.

70. IeDEA-SA. International Epidemiologic Databases to Evaluate Aids Southern Africa. [14/06/2013]; Available from: http://www.iedea-sa.org/index.php?id=2732.

PART C: JOURNAL READY MANUSCRIPT

Outcomes of infants starting Antiretroviral Therapy in Southern Africa, 2004-2012.

Mireille Porter*[1], MB ChB (UCT)

[1]School of Public Health and Family Medicine, University of Cape Town, Faculty of Health Sciences, Falmouth Building, Anzio Road, Observatory, Cape Town, 7925 South Africa

***Corresponding author email address**: mireilleporter@gmail.com

Conflicts of interest and Sources of Funding: This study was supported by the National Institute of Allergy and Infectious Disease (NIH) and the Eunice Kennedy Shriver Institute of Child Health and Human Development (Grant number: 2U01AI069924). The funders did not participate in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript. The authors have no other funding or conflicts of interest to disclose.

Word count: 3478 words
Abstract: 248 words
Tables: 2
Figures: 3
Keywords: infants, antiretroviral therapy, outcomes, Southern Africa.

The following journal manuscript is in keeping with requirements as stated in the Instructions for Authors of The Pediatric Infectious Disease Journal (Appendix F).
The following deviations from journal requirements have been made in keeping with instructions for the mini-dissertation.

1. Figures and tables have been inserted in the text of the dissertation rather than separately submitted as required by the journal. Formatting of tables has been altered to accommodate for in text inclusion.
2. Supplementary material referred to in the article has been inserted in the appendices as Appendix G of the mini-dissertation.
3. Co-authors have not been listed however their contributions, including that of Supervisors, have been noted in the acknowledgements section of the mini-dissertation.

Abstract

Background: There is limited published data on the outcomes of infants starting antiretroviral therapy (ART) in routine care in Southern Africa. This study aimed to examine these outcomes together with the baseline characteristics of infants at ART initiation.

Methods: Analysis of prospectively collected cohort data from routine ART initiation in infants at 11 sites contributing to the International Epidemiologic Database to Evaluate AIDS in Southern African was done. ART naïve HIV-infected infants <12 months of age at initiation of ≥ three antiretroviral drugs after 2003 were included. Kaplan-Meier estimates were calculated for mortality, loss to follow-up (LTFU), transfer out and virological suppression. Cox Proportional Hazards models stratified by site were used to determine baseline characteristics associated with outcomes mortality and virological suppression.

Results: The median (interquartile range (IQR)) age at ART initiation of 4945 infants was 5.9 months (3.7-8.7) with median (IQR) follow-up of 11.2 months (2.8-20.0). At ART initiation 87% were severely immunosuppressed (World Health Organisation (WHO) 2006 definition) and 77% had WHO clinical stage 3/4 disease. Three-year mortality probability was 15.9% and LTFU 28.9%. Severe immunosuppression, WHO stage 3/4, anaemia, being severely underweight and initiation of treatment prior to 2010 were associated with worse mortality outcomes. At 12 months from ART initiation the proportion of infants severely immunosuppressed was 17% and the probability of attaining virological suppression was 56.1%.

Conclusion: Most infants initiating ART in Southern Africa had severe disease. Infant immunological and virological responses were suboptimal and high levels of LTFU and mortality were seen.

Introduction

Despite advances in Prevention of Mother to Child Transmission (PMTCT) programs, including possible reduction of vertical transmission to as low as 1% 2011 saw over 900 HIV infected infants born daily, the vast majority in sub-Saharan Africa.[1,2] Infants differ from older children and adults with respect to rapid physical growth (especially of their developing brain), establishment of a functioning immune system and a rapidly changing physiology. [3-5] Furthermore infants infected with HIV experience an increased vulnerability to the multiple insults of the virus and its complications [6,7] including accelerated disease progression and an increased risk of morbidity and mortality. [8-12] These worsened outcomes, together with age-specific diagnostic, [5,13] treatment and monitoring [8] challenges as well as neglect in advances in paediatric HIV policy, pharmaceuticals and testing, make infants a high risk population. [5, 13-15]

2008 saw changes to international guidelines for the initiation of antiretroviral therapy (ART) in infants where all infants below 12 months of age, regardless of immunological and clinical statuses previously used, were eligible for initiation of ART. [16] Subsequently the 2010 and 2013 guidelines were amended to provide ART for all children under 2 and under 5 years of age respectively [17,18] These changes were largely catalysed by evidence from experimental studies such as the Children with Human Immune Deficiency Virus Early Antiretroviral Therapy Trial (CHER). This trial, conducted in South Africa, quantified the benefits of early initiation of ART before 12 weeks of age in a 76% reduction in early infant mortality and 75% reduction in HIV progression when compared to deferring ART until World Health Organisation (WHO) 2006 treatment initiation criteria were met. [19,20]

With an average age at commencement of ART of 7 weeks, availability of appropriate laboratory testing and drug regimens including protease inhibitors, minimisation of loss to follow up and the exclusion of those with comorbid conditions or severe immunosuppression the features of this trial and its participants differ considerably from those within the resource-scarce routine care setting of Southern Africa. [5,13,15,20-23]

Literature pertaining to the outcomes of infants starting ART in routine care in resource scarce settings such as Southern Africa is limited and few studies include large numbers of infants starting ART after the WHO 2008 recommendation for immediate ART initiation in infants and the implementation thereof. Using data merged from the International Epidemiologic Database to Evaluate AIDS in Southern Africa (IeDEA-SA) sites this study aimed to describe baseline characteristics of infants starting first line ART in routine care settings within Southern Africa, their treatment outcomes including clinical, immunological and virological responses and to identify the determinants for these outcomes.

Methods

Study design and population

We conducted a retrospective analysis of prospectively collected cohort data of infants that initiated ART in routine care settings between January 2004 and December 2012 at sites contributing to the IeDEA-SA collaboration.[24] Data for this collaborative cohort is captured on site by site investigators through the routine clinical follow up of infants within the standard treatment and monitoring of HIV and ART and anonymised data is then transferred to the central IeDEA-SA datacenter using a Data Transfer Protocol.

This analysis included 11 sites from South Africa, Zimbabwe, Malawi and Zambia. Site inclusion required the initiation of infants on ART both before and after 1 January 2010 so as to as to ensure that each cohort captured a portion of infants initiated after the release of the WHO 2010 guidelines for early initiation. [25] HIV–infected (recorded Polymerase chain reaction (PCR) diagnosis or presumptive diagnosis); ART-naive (except for PMTCT exposure) infants with a recorded date of initiation of at least 3 antiretroviral drugs before the age of 12 months were eligible for inclusion. Participants with missing data for date of initiation of ART, age and gender were excluded from the analysis as were those infants identified as being virologically suppressed (HIV-Ribonucleic Acid (RNA) <400 copies/ml) due to the suggestion of possible non-naivety to ART. Eligibility for ART initiation was site specific and would reflect the country's guidelines at the time and the level of implementation of such guidelines. [26]

Each site has institutional ethical approval for contribution of data to IeDEA-SA Ethical approval for the database and this analysis was obtained from the Health

Sciences Human Research Ethics Committee of the University of Cape Town, South Africa.

Key cohort characteristics and outcomes

Characteristics of infants at initiation of ART included demographic details, anthropometric measures, haemoglobin (Hb), clinical (WHO clinical staging) [27] ,immunological and virological markers of disease severity and information pertaining to medicines administered including PMTCT therapy. These characteristics are presented overall and according to time period (before or after 1 January 2010) of initiation. P values are reported as per significance testing for the differences between medians (Wilcoxon Sum Rank Test) and differences between proportions.

Where not recorded for day of initiation the measurements from the closest date to initiation within an interval 6 months prior and 1 week post initiation was used for laboratory baseline characteristics and 3 months prior and up to day of initiation for anthropometric characteristics. Age at ART initiation was categorised as <3 months, 3-6 months and 6-12 months. Severe anaemia was defined using the Division of AIDS (DAIDS) guidelines [2] Hb <10g/dL where age in days was ≤ 21; <8g/dL for those 22-35 days and Hb <7g/dL for those age 36-56 days and <7.5g/dl for those age ≥57days. Weight and height measures were converted to age and gender specific z-scores (weight-for-age z-score (WAZ), height-for-age z-score (HAZ) and weight–for-height (WFHZ) using the 2007 WHO growth reference standards [29] WAZ and HAZ were further each categorised as <-3, -3 to -2 and >-2. Severe immune suppression was defined where the lowest of the CD4 absolute cell count or percentage met classification as the as per the WHO criteria. [27] Virological

suppression was defined on the first date of a recorded viral load <400 copies/ml. Year of initiation was defined before 2010 or 2010 and after so as to reflect the 2010 WHO changes to guidelines for initiation of ART [25] and a time where the 2008 WHO guidelines were implemented at national levels.

Death, transfer out (TFO), loss to follow-up (LTFU) and virological suppression were assessed as outcomes. LTFU was defined where the last visit recorded was more than 9 months prior to site database closure with the date of LTFU being the date of the last visit. Response variables included CD4 absolute cell count and percentage, viral load and anthropometric measures (WAZ and HAZ).

Statistical methods

Descriptive analyses of baseline characteristics of infants at initiation of ART and responses over time are provided in accordance with the variable format and distribution. Immunological, virological and anthropometric responses over time on ART were examined in those infants who remained in care for a minimum of 12 months. This was done so as to approximate a true change in averages by minimising the effect of loss (through death, LTFU) of the sicker infants on these averages.

Survival Analysis using the Kaplan-Meier method was used to assess time to event data for outcomes of mortality, TFO, LTFU and virological suppression. Competing Risk Analysis provided Cumulative Incidence Functions considering death, TFO and LTFU. Cox Proportional Hazards models stratified by site were used to determine baseline characteristics associated with mortality with a separate model including estimates for baseline virological characteristics within South African sites. This was done due to the high levels of missing virological data from sites outside South Africa. Cox Proportional Hazards models stratified by site were used to determine

baseline characteristics associated with time to virological suppression in a cohort comprised only of infants from South African sites whom had a baseline viral load and at least 1 other follow up viral load measurement recorded.

Missing baseline data for CD4 count and percent, Hb, WAZ and HAZ and WHO stage were modelled using multiple imputation. The imputation model, with the assumption of data missing at random, included all baseline characteristics including site, age and year of initiation, outcomes of mortality, LTFU and TFO and follow-up time. Five imputation sets were generated and reported estimates representing pooled imputed data estimates were calculated using Rubin's Rules. [30]

Independent variable for inclusion in the models were selected *a priori* and are complemented by a post-imputation model selection method using Variable Importance (VI) and an estimate weighted according to both frequency and strength of association in the augmented datasets. [31]

All statistical analysis was done using STATA 12.0 [32] with multiple imputation done using ICE.

Results

Cohort characteristics

The median (Interquartile range (IQR)) age at ART initiation of 4945 infants was 5.9 months (3.7;8.7) with median follow-up of 11.2 months (IQR 2.8;20.0). Amongst the 11 sites represented in this cohort, together demonstrating all levels of care, 8 South African sites contributed 3473 (70%) of infants. 26% of the total cohort represented infants initiating ART after 2009.

Baseline Characteristics

At ART initiation 76.5% of infants were classified as WHO clinical stage 3/4 and 87.2% met the 2006 WHO definition of severe immunosuppression (Table 1). Approximately 60% of infants were either moderately of severely underweight and approximately 60% were either moderately or severely stunted at initiation. A baseline viral load measure was only recorded for 41.3% of infants in the total cohort, with median viral load of 5.99 log 10 copies/ml (IQR 5.41;6.45).

Infants initiating ART after 2009 were generally younger and less severley ill than those initiating in 2009 and before suggesting that a proportion of infants started on ART after 2009 were started without severe disease (Table1).

Missing data of baseline characteristics was seen in all anthropometric and laboratory measures with the highest prevalence seen in virological data (Table 1).

Table 1. Baseline characteristics of infants initiating ART, 2004-2012

Characteristics	N	Overall*	2004-2009	2010-2012	p value
Age (months), median (IQR)	4945	5.98 (3.68;8.74)	6.11 (3.81;8.87)	5.42 (3.35; 8.38)	0.0000
Female, n(%)	4945	2546 (51.49%)	1845 (50.69%)	701 (53.72%)	0.0603
WHO stage 3 or 4, n (%)	4347	3327 (76.54%)	2605 (81.18%)	722 (63.44%)	0.0000
Absolute CD4, median (IQR)	3417	765 (347;1334)	724 (324;1274)	887 (440;1535)	0.0000
CD4 Percentage, median (IQR)	3244	18.45 (12;26)	18 (11.5;24.9)	20.7 (13.6;28.4)	0.0000
Severe Immunosuppression (WHO 2006), n (%)	3514	3063 (87.17%)	2336 (89.16%)	727 (81.32%)	0.0000
Viral Load ≥1 000 000, n (%)	2042	1012 (49.56%)	815 (49.54%)	197 (49.62%)	0.9777
Severe Anaemia (DAIDS 2009), n (%)	2813	248 (8.82%)	176 (8.74%)	72 (9.01%)	0.8182
Weight-for-age z – score (WAZ), median (IQR)	3795	-2.53 (-3.96;-1.16)	-2.69 (-4.12; -1.34)	-2.12 (-3.45;-0.84)	0.0000
WAZ category, n (%)	3795				
WAZ > -2		1523 (40.13%)	1.037 (37.13%)	486 (48.31%)	0.0000
WAZ ≤ -2 to > -3		686 (18.08%)	510 (18.29%)	176 (17.50%)	0.5762
WAZ ≤ -3		1586 (41.79%)	1242 (44.53%)	344 (34.19%)	0.0000
Height–for–age z-score (HAZ), median (IQR)	2919	-2.50 (-3.90;-1.12)	-2.64 (-4.01;-1.28)	-2.16 (-3.54;-0.77)	0.0000
HAZ category, n (%)	2919				
HAZ > -2		1177 (40.32%)	844 (38.59%)	333 (45.49%)	0.0010
HAZ ≤ -2 to > -3		538 (18.43%)	392 (17.92%)	146 (19.95%)	0.2222
HAZ ≤ -3		1204 (41.25%)	951 (43.48%)	253 (34.56%)	0.0000

First Line Regimen, n (%)	4653	
D4T + 3TC + lopinavir/ritonavir		2068 (44.44%)
D4T + 3TC + nevirapine		971 (20.87%)
ABC + 3TC + lopinavir/ritonavir		598 (12.85%)
AZT + 3TC + nevirapine		343 (7.37%)
AZT + 3TC + lopinavir/ritonavir		286 (6.15%)
Other		387 (8.32%)
3rd ART drug, n (%)	4659	
lopinavir/ritonavir		2957 (63.47%)
ritonavir		214 (4.59%)
nevirapine		1399 (30.03%)
efavirenz		89 (1.91%)
PMTCT exposure, n (%)	1637	
Exposed		948 (57.91%)

D4T: stavudine, 3TC:lamivudine, ABC: abacavir, AZT: zidovudine

**Proportions represent proportion of non-missing (N) observations*

Mortality and programmatic outcomes

Mortality was highest in the few months after ART initiation with 6 and 12 month cumulative probabilities of 10.1% (95% Confidence Interval (CI) 9.3-11.1) and 13.2% (95% CI 12.1-14.3) respectively (Figure1a). Cumulative probabilities of being LTFU showed a considerable loss in the first year with 6 and 12 months probabilities of 13.7% (95% CI 12.7-14.7) and 18.8% (95% CI 17.6-20.1) respectively (Figure1a). Transfer out from a higher level of care to another facility occurred throughout follow-up with the 36 month probability being 34.2% (95% CI 32.3-36.1) (Figure1a). Analysis of these outcomes using the cumulative incidence functions from a competing risk analysis provided a 12 month probability of mortality (competing with LTFU and TFO) of 11.3% (95% CI 10.4-12.2) (Figure 1b). The correlating probabilities of being alive and in care at 6 and 12 months were 71.5% (95% CI 70.2-72.7) and 59.6% (95% CI 58.2-61.0) respectively.

Unadjusted assessment of the outcome mortality according to time period of initiation suggested improved mortality in those initiating ART in the year 2010 and onwards (Log-rank test for equality of survivor functions p= 0.0005). The apparent lower mortality from 2010 onwards was unlikely to be due to lower ascertainment of deaths in the later period, as there was a trend towards lower LTFU from 2010 onwards in comparison to the preceding years (Log-rank test for equality of survivor functions for LTFU between time period prior to 2010 and period 2010 onwards p=0.0567) (Figure 1c and 1d).

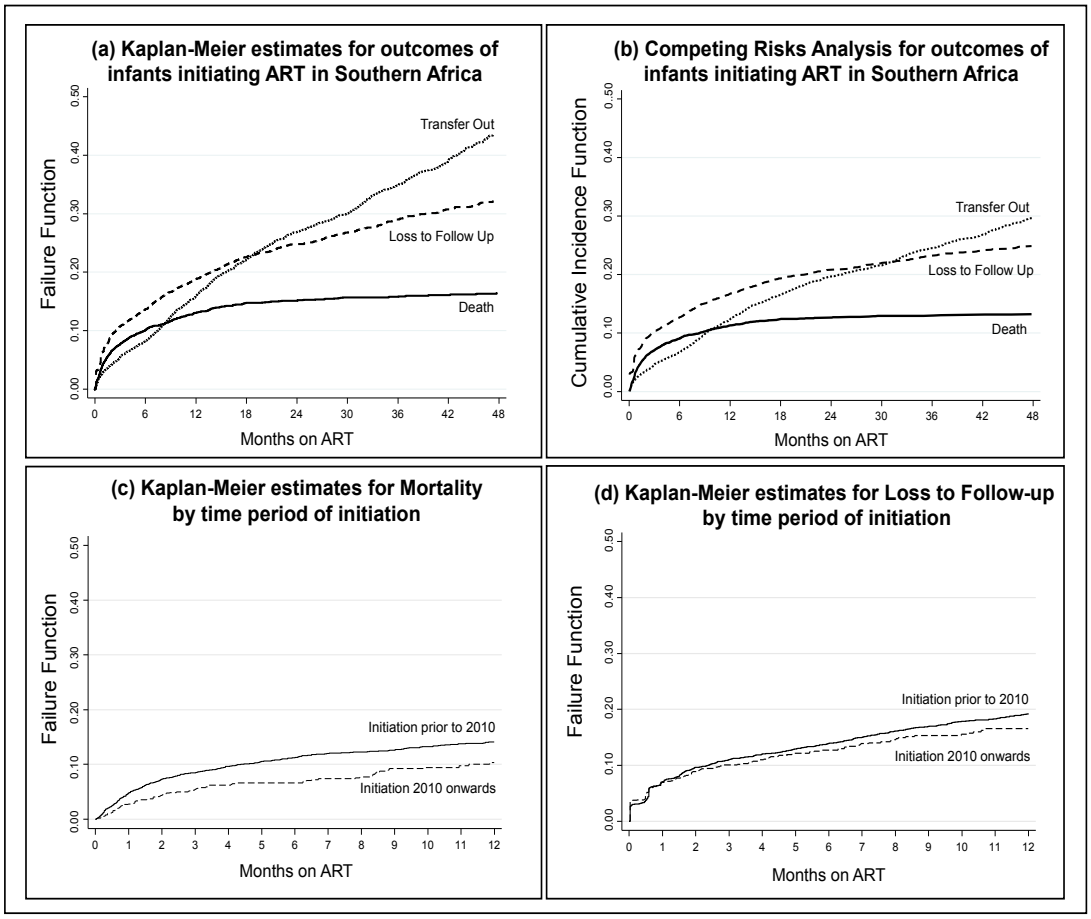


Figure 1. Kaplan-Meier failure functions and competing risk cumulative incidence functions of time to outcomes of death, LTFU and TFO over time on ART including in graphs (c) and (d) failure functions of death and LTFU by time period of initiation.

Baseline Characteristics associated with mortality

Severe immunosuppression (adjusted Hazard ratio (aHR) 2.19, 95% CI 1.44-3.33), WHO stage 3/4 (aHR 1.36, 95% CI 1.04-1.78), lower weight-for-age z-score and initiation of ART in 2010 or after were each found to be independently associated with mortality (Table 2). Compared to having a WAZ of >-2 those infants with WAZ <-3 at baseline had a 2.23 fold (aHR, 95% CI 1.78-2.80) increase in the hazard of an earlier time to death. After adjusting for factors of disease severity at baseline, infants initiating ART in 2010 or later had a reduced risk of death compared to those

initiated before 2010 (aHR 0.75, 95% CI 0.59-0.94). No evidence was found supporting an effect on mortality of infant age group. Overall estimates from the imputed datasets using Rubin's Rules provided similar estimates to those of the complete case analysis (Supplementary table 1 and 2).

In an analysis restricted to infants from SA sites, there was no association between baseline viral load category and death after adjustment for other disease severity characteristics at baseline (Supplementary Table 2).

Table 2. Survival Analysis of imputed data: Cox regression for predictors of mortality stratified by cohort

	Univariate			Multivariate*			Model Selection ¥		
Variable	**HR**	**P value**	**95% CI**	**HR**	**P value**	**95% CI**	**HR**	**95% CI**	**VI**
Female gender	0.97	0.716	0.83-1.14	-	-	-	-	-	0.31
Age at Initiation 0-3 months	reference			reference			reference		
Age at Initiation 3-6 months	0.90	0.417	0.71-1.15	0.87	0.268	0.68-1.11	-	-	0.22
Age at Initiation 6-12 months	0.98	0.898	0.78-1.25	0.84	0.161	0.66-1.07	-	-	-
Severe Immune suppression (WHO 2006)	2.51	0.000	1.66-3.79	2.19	0.000	1.44-3.33	2.15	1.42-3.27	1
WHO stage 3 or 4	1.89	0.000	1.47-2.45	1.36	0.023	1.04-1.78	1.35	1.04-1.77	0.87
Severe Anaemia (DAIDS 2009)	1.57	0.003	1.18-2.10	1.34	0.062	0.98-1.82	1.29	0.82-2.05	0.79
Weight-for-Age (Z-score) > -2	reference			reference			reference		
Weight-for-Age (Z-score) -2 to -3	1.40	0.015	1.07-1.84	1.29	0.063	0.99-1.71	1.29	0.99-1.71	1
Weight-for-Age (Z-score) < -3	2.55	0.000	2.04-3.19	2.23	0.000	1.78-2.80	2.22	1.78-2.79	-
ART Initiated 2010 and after	0.65	0.000	0.52-0.83	0.75	0.015	0.59-0.94	0.75	0.59-0.95	0.88
***** Viral Load > 1 million**	1.30	0.045	1.01-1.68	1.17	0.267	0.88-1.56	1.14	0.79-1.62	0.56

*Adjusted for age, weight-for-age category, severe immunosuppression, WHO stage 3/4, severe anaemia and initiation after 2009

***modelled on a subset of infants from South African cohorts, adjusted for variables as above

¥ Using AIC and Variable Importance (VI)

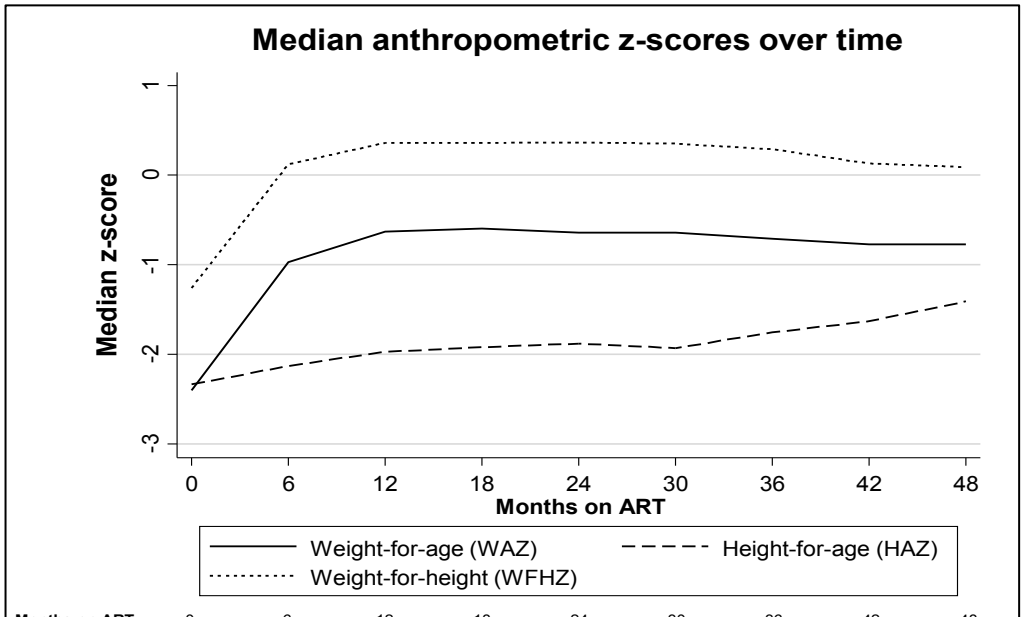
HR: Hazard Ratio

CI: Confidence Interval

Response on ART for infants remaining in care for a minimum of 12 months

Anthropometric Response

Weight-for-age showed rapid improvement in the first 6 months of therapy with an increase from a median WAZ of -2.40 to -0.97 (Figure 2). Height-for-age showed a slower progression reaching a median HAZ of -1.97 from a baseline of -2.34 after 1 year on ART.



Months on ART	0	6	12	18	24	30	36	42	48
Weight-for-age									
n	1775	1920	1871	1572	1252	984	791	603	465
Median	-2.40	-0.97	-0.63	-0.59	-0.64	-0.64	-0.71	-0.77	-0.77
IQR	-3.85;-1.02	-2.06;0.01	-1.55;0.29	-1.53;0.27	-1.51;0.16	-1.46;0.07	-1.44;-0.06	-1.47;-0.04	-1.45;-0.08
Height-for-age									
n	1418	1700	1649	1385	1106	858	694	518	397
Median	-2.34	-2.13	-1.97	-1.92	-1.88	-1.93	-1.76	-1.63	-1.41
IQR	-3.76;-1.02	-3.37;-1.04	-3.09;-0.99	-2.96;-0.96	-2.83;-0.88	-2.67;-0.93	-2.55;-0.90	-2.41;-.077	-2.32;-0.60
Weight-for-height									
n	1412	1696	1648	1385	1102	856	691	514	391
Median	-1.26	0.12	0.36	0.36	0.37	0.35	0.29	0.13	0.09
IQR	-2.73;0.15	-1.01;1.13	-0.56 ;1.31	-0.51;1.29	-0.45;1.22	-0.41;1.15	-0.52;1.06	-0.52;1.06	-0.68;1.06

Figure 2. Growth response on ART over time for infants remaining in care for at least 1 year.

Immunological Response

Absolute CD4 count showed a rapid increase in the first year after initiation with a 12 month median CD4 cell count of 1573 cells/mL being almost double that seen at baseline (Figure 3a). As expected CD4 percentages, a measure adjusting more appropriately for age-related immunological changes, showed a similar initial trend but with a sustained increase in median values only reaching a plateau at 36 months (Figure 3b). These combined effects can be seen in the change in the proportion of infants meeting the WHO criteria for severe immune suppression with a change from 87.1% (95% CI 85.5-88.7) at baseline to 16.6% (95% CI 14.8-18.4) at 12 months and 3.0% (95% CI 1.8-4.3) at 36 months.

Haemoglobin

Median (IQR) haemoglobin increased from a baseline of 9.7 g/dL to 11 g/dL (10.2; 12.0) at 6 months (Figure 3c).

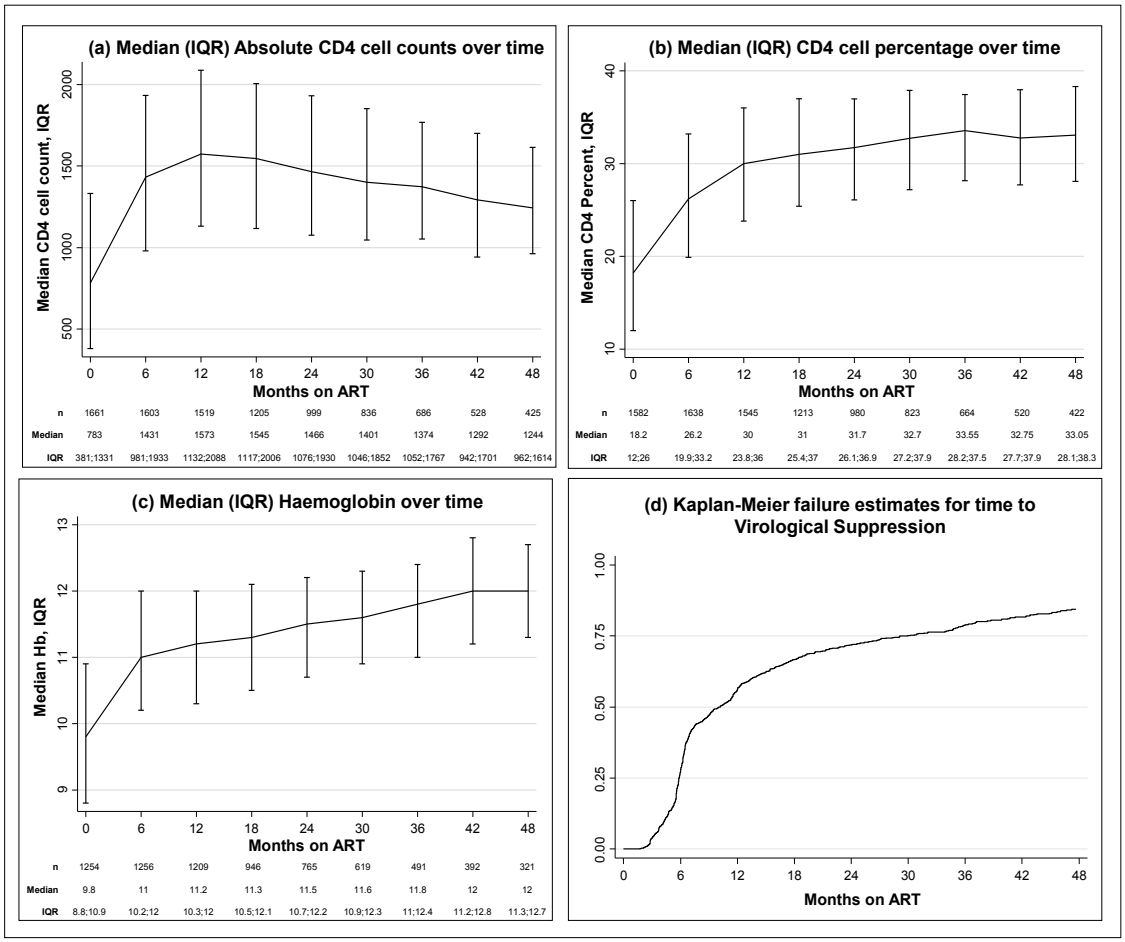


Figure 3. Responses over time on ART of a) Changes in median CD4 Absolute Cell counts , b) Changes in median CD4 Percentage, c)changes in median Haemoglobin over time and d) Kaplan-Meier estimates for outcome of Virological suppression in a subset if South African infants with s minimum of a baseline and one other viral load measurement.

Virological response

Amongst a subset of infants from South African sites who had a minimum of a baseline and one other viral load measurement the probabilities of attaining virological suppression at 6 and 12 months were found to be 28.1% (95% CI 25.6-30.7) and 56.1% (95% CI 53.2-59.1) respectively (Figure 3d). The only independent predictor of failure to suppress was a viral load of 1 million copies/ml or above at ART start (aHR 0.78, 95%CI 0.68-0.89) (Supplementary table 3).

Discussion

Principle findings

In this study we found that infants initiating ART in Southern Africa between 2004 and 2012 had a high median age and a high predominance of severe baseline disease severity, with some improvement after 2009. Within this cohort we noted that despite considerable early responses to ART and a reduction in the prevalence of severe disease characteristics, infants remaining in care experienced suboptimal immunological, anthropometric and virological responses. Furthermore mortality, particularly in the initial stage after ART initiation, was high and loss to follow-up was substantial throughout the observation period. Analysis of those factors independently associated with mortality identified baseline immunological, clinical and anthropometric characteristics together with the time period of initiation of ART, where initiation after 2009 was found to have a protective effect.

Strengths and Limitations of findings

To our knowledge this is the largest study of infant ART outcomes in Sub-Saharan Africa to date. Observing HIV infected infants over a period of time of considerable guideline changes this study includes infants from several Southern African sites, each representing the routine provision of HIV care and together representing all levels of health care. The levels of missing data were most noted in virological measures. This was due to the unavailability of these measures beyond South Africa and the use of virological measures for confirmation of HIV diagnosis within South Africa.

The use of multiple imputation in the management of missing baseline data has resulted in avoidance of bias associated with complete case analysis. [33,34]

The advanced age at initiation observed in this study, although representing the reality of the routine care setting, is likely to have resulted in survival bias through the formation of a cohort of survivors. This survival effect, worse in older infants by virtue of having survived longer, would result in a reduction of any potential benefit of starting ART at a younger age and may be responsible for failure to observe an age effect in this study.

Beyond inability to observe associations for variables such as comorbidities, infant feeding practices, PMTCT, cotrimoxazole prophylaxis and socio-economic factors which were poorly collected or absent, lack of data on these variables may have resulted in residual confounding. Furthermore associations between regimen and outcomes were not examined due to a near perfect correlation with site/country of origin. Concern also exists pertaining to the possibility of the under-ascertainment of mortality in view of the high proportion of infants lost to follow-up. An increased rate of loss to follow-up was not observed for the period after 2009 and suggests differential loss to follow-up (with regards to year of initiation) did not affect the validity of the association between year of initiation and mortality.

Electronic data capturing procedures necessary for site inclusion in the IeDEA-SA databases may have resulted in a reduction in data representivity for all routine care sites within Southern Africa.

Interpretation

The CHER trial, possibly the most significant contributor for evidence for the early initiation of ART in infants, showed the benefits of early ART in a cohort of infants with a very young age and complete absence of severe immunosuppression at baseline. [20] The low likelihood of fully achieving these benefits within the South African routine care setting due to suboptimal coverage of early infant HIV diagnosis was highlighted by Johnson et al (2012) in a model-based analysis examining the effect of early ART provision.[35] Our study has confirmed through observation what this analysis suggested – that within the context of delayed initiation infant ART outcomes are suboptimal. The predominance of severe baseline disease and failure to attain levels of normality in immunological, anthropometric and virological responses as well as high levels of mortality and loss to follow-up are cause for considerable concern. Furthermore with an estimated 45% of in utero-infected and 22% of intrapartum-infected infants dying or lost to follow-up by 14 weeks of age our concern is extended to the uncaptured pre-ART losses seen with delayed initiation. [36]

This study has briefly described the improvements in delay in initiation over time, a trend seen in comparing earlier observational studies from Sub-Saharan Africa to more recent studies. These observed improvements over time include a reduction in age at initiation,[21,37] baseline disease severity and outcomes of mortality.[9,21] Our results are also comparable to those observed in more recent studies pertaining to immunological [38,39] and anthropometric responses [21,40] and mortality [41] in infants on ART within sub-Saharan Africa. Our findings relating to virological suppression vary considerably to those of previous studies such as Kay et al (2012) who described a 45% 12 month probability of virological suppression (defined as two

consecutive viral load <400copies/ml) and to Tukei et al (2013) who described a 12 month probability of virological suppression of 72% in a cohort of infants with minimum of 6 months of ART.[21,42] These differences are likely to be largely due to the population and treatment program dissimilarities in these studies.

Beyond the change in characteristics over time our study has identified the effect of initiation of ART from 2010 onwards (when early initiation was implemented on a national scale) – with improved outcomes of mortality over and above that expected to be associated with improvements in age and baseline characteristics. This highlights the role of an uncaptured element of improved baseline disease severity and programmatic advances and suggests that the implementation of the guidelines for early initiation may have resulted in an improvement in the outcomes of these infants through a greater urgency and attention toward infant ART initiation.

Recommendations

Ongoing attention to the initiation and continued management of ART in infants is required for the optimisation of care and outcomes of these infants. Efforts towards approximation of the early initiation standards set by the trials upon whose evidence guidelines for early initiation were based could reduce the currently persisting vulnerability of infants on ART. Research is therefore necessary to identify how to overcome barriers to early initiation and optimal care of HIV infected infants including issues of PMTCT linkage, birth testing, infant ART initiation and maintenance, and the reduction of loss to follow-up.

Conclusion

In a large cohort of HIV infected infants within the routine care setting of Southern Africa we observed improvements in disease severity characteristics at ART initiation and outcomes on ART. While there has clearly been progress with regard to timely initiation of infants on ART and consequently improved outcomes, this remains inadequate as delayed initiation results in severe baseline illness and the persistence of a vulnerability of infants despite the administration of ART.

Acknowledgments

We would like to thank every child who has contributed data to this research, their caregivers, health care providers at participating sites as well as all staff involved in the preparation of data contributed to the IeDEA-SA Southern African Collaboration.

We would like to thank staff at the IeDEA-SA Cape Town office: Morna Cornell, Nicola Maxwell, Leigh Johnson and special thanks to Michael Schomaker for his valuable insight and assistance in the analysis. We would also like to thank the IeDEA-SA Bern office with special thanks to Fritz Kaeser, Claire Graber and Kelly Goodwin for their roles in data management and project management respectively.

Funding: This study was supported by the National Institute of Allergy and Infectious Disease and the Eunice Kennedy Shriver Institute of Child Health and Human Development (Grant number: 2U01AI069924).).

The funders did not participate in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript.

References

1. UNAIDS. Report on the global AIDS epidemic 2010: Available from: http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf.

2. UNICEF. Towards an AIDS-Free Generation 2012: Available from: http://www.unicef.org/aids/files/hiv_InfographicREV2.pdf.

3. UNICEF. HIV and AIDS. Eastern and Southern Africa. . 2013 [updated 2012; cited 2013 14 October]; Available from: http://www.unicef.org/esaro/5482_HIV_AIDS.html.

4. World Health Organisation. Early detection of HIV infection in infants and children. Guidance note on the selection of technology for the early diagnosis of HIV in infants and children. Summary of recommendations. . 2007: Available from: http://www.who.int/hiv/paediatric/EarlydiagnostictestingforHIVVer_Final_May07.pdf.

5. DNDi. Drugs for Neglected Diseases Initiative. 2013 [cited 2013 14/06/2013]; Available from: http://www.dndi.org/diseases-projects/diseases/paediatric-hiv.html.

6. World Health Organisation W. Children are not little adults, Children's Health and the Environment. WHO Training Package for the Health Sector. 2008: Available from: http://www.who.int/ceh/capacity/Children_are_not_little_adults.pdf.

7. Puthanakit T, Bunupuradah T. Early versus deferred antiretroviral therapy in children in low-income and middle-income countries. Curr Opin HIV AIDS. [Review]. 2010 Jan;5(1):12-7.

8. Chiappini E, Galli L, Tovo P-A, et al. Virologic, immunologic, and clinical benefits from early combined antiretroviral therapy in infants with perinatal HIV-1 infection. Official Journal of the International AIDS Society2006;20(2):207-15.

9. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. Journal of the American Medical Association2007 Oct 24;298(16):1888-99.

10. Fetzer BC, Hosseinipour MC, Kamthuzi P, et al. Predictors for mortality and loss to follow-up among children receiving anti-retroviral therapy in Lilongwe, Malawi. Trop Med Int Health2009 Aug;14(8):862-9.

11. Davies M-A, Keiser O, Technau K, et al. Outcomes of the South African National Antiretroviral Treatment Programme for children: The IeDEA Southern Africa collaboration. South African Medical Journal2009(99):730-7.

12. Dunn DG, D.M; Duong, T Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. The Lancet2003;362(9396):1605-11.

13. Lallemant M, Chang S, Cohen R, Pecoul B. Pediatric HIV — A Neglected Disease? New England Journal of Medicine2011;365(7):581-3.

14. Prendergast AJ, Penazzato, M., Cotton, M., Musoke, P., Mulenga, V., Abrams, E.J., Gibb, D.M.,. Treatment of Young Children with HIV Infection: Using Evidence to Inform Policymakers. PLoS Med 2012;9(7):e1001273.

15. Prendergast A, Mphatswe W, Tudor-Williams G, et al. Early virological suppression with three-class antiretroviral therapy in HIV-infected African infants. Official Journal of the International AIDS Society2008 Jul 11;22(11):1333-43.

16. World Health Organisation. Report of the WHO Technical Reference Group: WHO Antiretroviral Therapy for Infants and Children 2008 ,. 2008: Available from: http://www.who.int/hiv/pub/paediatric/WHO_Paediatric_ART_guideline_rev_mreport_2008.pdf.

17. World Health Organisation W. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013: Available from: http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html.

18. World Health Organisation. Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector. 2010; (05/08/2013): Available from: www.who.int/hiv/pub/2010progressreport/summary_en.pdf.

19. World Health Organisation W. Antiretroviral therapy of HIV infection in infants and children Recommendations for a public health approach (2006 revision). 2006: Available from: http://www.who.int/hiv/pub/paediatric/infants/en/index.html.

20. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. New England Journal of Medicine2008;359(21):2233-44.

21. Tukei VJ, Murungi M, Asiimwe AR, et al. Virologic, immunologic and clinical response of infants to antireteroviral therapy in Kampala, Uganda. BMC Pediatrics2013;13(42).

22. Hsiao NY, Stinson K, Myer L. Linkage of HIV-infected infants from diagnosis to antiretroviral therapy services across the Western Cape, South Africa. PLoS ONE2013;8(2):e55308.

23. Leroy V, Malateste K, Rabie H, et al. Outcomes of Antiretroviral Therapy in Children in Asia and Africa: A Comparative Analysis of the IeDEA Pediatric Multiregional Collaboration. Journal of Aquired Immune Deficiency Syndrome2013(62):208-19.

24. IeDEA-SA. International Epidemiologic Databases to Evaluate Aids Southern Africa. [14/06/2013]; Available from: http://www.iedea-sa.org/index.php?id=2732.

25. World Health Organisation. Antiretroviral Therapy For HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a public health approach. 2010 revision. 2010: Available from: http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf.

26. Davies MA, Phiri S, Wood R, et al. Temporal trends in the characteristics of children at antiretroviral therapy initiation in southern Africa: the IeDEA-SA Collaboration. PLoS ONE2013;8(12):e81037.

27. World Health Organisation. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children 2007: Available from: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf?ua=1.

28. Division of AIDS (DAIDS). Table for Grading the severity of adult and pediatric adverse events. 2009; Available from: http://rsc.tech-res.com/document/safetyandpharmacovigilance/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf.

29. World Health Organisation. WHO Child Growth Standards based on length/height, weight and age. 2006; 450: Available from: www.ncbi.nlm.nih.gov/pubmed/16817681.

30. Rubin DB. Multiple Imputation After 18+ Years. Journal of the American Statistical Association1996;91(434):473-89.

31. Schomaker M, Heumann C. Model selection and model averaging after multiple imputation. Computational Statistics and Data Analysis2014;71:758-70.

32. StataCorp. STATA 12. In: StataCorp, editor. Texas: StataCorp LP; 2011.

33. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Statistics in Medicine1999 Mar 30;18(6):681-94.

34. Patrician PA. Multiple imputation for missing data. Research in Nursing and Health2002 Feb;25(1):76-84.

35. Johnson LF, Davies MA, Moultrie H, et al. The effect of early initiation of antiretroviral treatment in infants on pediatric AIDS mortality in South Africa: a model-based analysis. The Pediatric Infectious Disease Journal. [Research Support, Non-U.S. Gov't]. 2012 May;31(5):474-80.

36. Lilian RR, Kalk E, Bhowan K, et al. Early diagnosis of in utero and intrapartum HIV infection in infants prior to 6 weeks of age. J Clin Microbiol. [Evaluation Studies Research Support, N.I.H., Extramural, Non-U.S. Government]. 2012 Jul;50(7):2373-7.

37. KIDS ART LINC. Low risk of death, but substantial program attrition, in pediatric HIV treatment cohorts in Sub-Saharan Africa. Journal of Acquired Immune Deficiency Syndrome2008 Dec 15;49(5):523-31.

38. Purchase SE, Van der Linden DJ, McKerrow NH. Feasibility and effectiveness of early initiation of combination antiretroviral therapy in HIV-infected infants in a government clinic of Kwazulu-Natal, South Africa. J Trop Pediatr2012 Apr;58(2):114-9.

39. Meyers TM, Yotebieng M, Kuhn L, Moultrie H. Antiretroviral therapy responses among children attending a large public clinic in Soweto, South Africa. Pediatric InfectIous Diseases Journal2011 Nov;30(11):974-9.

40. Feinstein L, Yotebieng M, Moultrie H, Meyers T, Van Rie A. Effect of baseline immune suppression on growth recovery in HIV positive South African children receiving antiretroviral treatment. Journal of Acquired Immune Deficiency Syndrome2012 Oct 1;61(2):235-42.

41. McNairy ML, Lamb MR, Carter RJ, et al. Retention of HIV-infected children on antiretroviral treatment in HIV care and treatment programs in Kenya,

Mozambique, Rwanda, and Tanzania. Journal of Acquired Immune Deficiency Syndrome2013 Mar 1;62(3):e70-81.

42. Kay J, Wanzira H, Sandison T, et al. Virologic suppression in nevirapine-exposed HIV-infected infants initiating antiretroviral therapy in rural Uganda. J Trop Pediatr. [Research Support, N.I.H., Extramural, Non-U.S. Goverment, U.S. Government, P.H.S.]. 2012 Jun;58(3):194-9.

Figure Legend

Figure 1.	a.	Kaplan-Meier estimates for outcomes of initiating ART in Southern Africa.
	b.	Competing Risk Analysis Cumulative Incidence Functions for outcomes of initiating ART in Southern Africa.
	c	Kaplan-Meier estimates for outcome of mortality by time period of initiation
	d	Kaplan-Meier estimates for outcome of loss to follow-up by time period of initiation
Figure 2.		Growth response on ART over time for infants remaining in care for at least 1 year.
Figure 3.	a.	Changes in median Absolute CD4 cell count over time on ART for infants remaining in care for a minimum of 12 months.
	b.	Changes in median CD4 percent over time on ART for infants remaining in care for a minimum of 12 months.
	c.	Changes in median Haemoglobin over time on ART for infants remaining in care for a minimum of 12 months.
	d.	Kaplan-Meier estimates of time to virological suppression.

PART D: APPENDICES

Appendix A: IeDEA –SA Data Transfer Protocol

STANDARD PROCEDURE FOR DATA TRANSFER

Version 2.0/ August 2010

Contents

1 Introduction 2

1.1 General remarks 2

1.2 Inclusion criteria for patients 3

1.3 Dates 4

1.4 Definitions 5

1.5 Standard codes 5

1.6 Data tables 6

2 Variables to be included in core tables 9

2.1 Socio-demographic characteristics and outcomes (PAT table) 9

2.2 Laboratory data (LAB table) 30

2.3 Antiretroviral drug variables (ART table) 32

2.4 Opportunistic events (OI table) 40

2.5 Follow-up clinic visits (VIS table) 43

3 Variables to be included in additional tables 45

3.1 Family and partner linkages (LINK table) 46

3.2 Pregnancy information (PREGNANCY table) 47

3.3 Parental Health (PAR_HEALTH table) 48

3.4 Tuberculosis information (TB table) 50

3.5 Trial/research study enrolment information (TRIAL table) 53

4 Revised Death (Outcome) data 54

5 Meta-data 55

Introduction

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, and 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.

- The use of UCT's Vula site is encouraged; this is an open-source tool allowing for the secure transfers of data from sites to the Data Centre. Vula is open and accessible 24 hours a day, 7 days a week.

- 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 anonymisation 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!

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.

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 appropriate.

- 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.

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).

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

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 patients 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. **OUTCOME_REVISED: (Death registry linkage data)** A table with information on updated death status following linkage to registry systems.

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

Variables to be included in core tables

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	Text & numeric characters (based on cohort/site/patient identifier - FS)	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	Sex / gender of patient

	ascertainment	
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
Name	Format and definitions	Description
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.
Name	Format and definitions	Description
FHV_STAGE_WHO	Numeric with codes: 1 = Stage I 2 = Stage II	Clinical WHO stage (I to IV) at time of starting HAART (Enter 88 patients who have not

	3 = Stage III 4 = Stage IV 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	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	Stage defining illness-3 at time of starting HAART. (Enter 88 patients who have not commenced HAART)

	ascertainment	
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)
Name	Format and definitions	Description
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	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

	recorded in ART table) 2 = Yes (MTCT exposed, drug history not reconstructable) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	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	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)

	ascertainment	
Name	Format and definitions	Description
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	
Name	Format and definitions	Description
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	Mode of delivery (paediatric patients only - enter 88 for adult patients)

	– emergency 22 = Caesarean section – type unknown 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	
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)
Name	Format and definitions	Description
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
6.1	Presumed heterosexual
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
Codes	Description	WHO stage (Adult)	WHO stage (Paed)	Event (Adult)	Event (Paed)	SDI (Adult)	SDI (Paed)
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
HZ*	Herpes zoster (not specified)	88	88	1	1	1	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
Codes	Description	WHO stage (Adult)	WHO stage (Paed)	Event (Adult)	Event (Paed)	SDI (Adult)	SDI (Paed)
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	88	88	1	1	0	0

	episode)						
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 Outcome
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

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)
Name	Format	Description
LAB_T	Text Lower than limit of detection for viral loads should be entered as	Text result eg. "> 6 000 000" or "P+++" Leave blank if result entered as number

	"LDL" TB microscopy and culture results should be entered as follows: - Paucibacillary 1+ 2+ 3+ Unknown +	(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)

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.
Name	Format	Description
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	Type of formulation

	1 = Tablet/capsule 2 = Syrup/Suspension 95 = Not ascertained 99 = Unknown despite attempting ascertainment	
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

Name	Format	Description
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)
J05A-BEV	Beviramat
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
ATC codes	Antiretroviral treatment
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-CPV	Capravirine
J05AG-ETV	Etavirine
J05AG-CPV	Capravirine
J05AG-LOV	Loviride
J05AG-RPV	Rilpivirine
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
J05AX07	Enfurvirtide (FUZEON, T-20/Ro 29-9800)

J05AX08	Raltegravir
JO5AX09	Maraviroc
J05AX-VIC	Vicriviroc
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

Note: Reasons for stopping treatment are grouped by similarity. The broad reason is indicated by the integer, while subcategories of that reason are denoted by figures to the right of the decimal point. Reasons should therefore be coded to the greatest level of detail that the data permits.

For example, if a drug was stopped because of treatment failure determined by a declining CD4 count, the stop reason should be coded as 1.3; however if the reason for stopping is

simply "treatment failure" with the means of determining this not specified, the stop reason should be coded as 1.

Old Code	Code*	Reason for treatment discontinuation	AE	CI	FL	Other
1	1	Treatment failure (i.e. virological, immunological, and /or clinical failure)			1	
1.1	1.1	Virological failure			1	
1.2	1.2	Partial virological failure			1	
1.3	1.3	Immunological failure – CD4 drop			1	
1.4	1.4	Clinical progression			1	
2	2	Abnormal fat redistribution	1			
3	3	Concern of cardiovascular disease	1			
3.1	3.1	Dyslipidaemia	1			
3.2	3.2	Cardiovascular disease	1			
4	4	Hypersensitivity reaction	1			
5	5	Toxicity, predominantly from abdomen/G-I tract	1			
5.1	5.1	Toxicity – GI tract	1			
5.2	5.2	Toxicity – Liver (ALT/Hepatitis)	1			
5.3	5.3	Toxicity – Pancreas	1			
6	6	Toxicity, predominantly from nervous system	1			
6.1	6.1	Toxicity - peripheral neuropathy	1			
	6.2	Toxicity - neuropsychiatric	1			
	6.3	Toxicity - headache	1			
7	7	Toxicity, predominantly from kidneys	1			
8	8	Toxicity, predominantly from endocrine system	1			
8.1	8.1	Diabetes	1			
9	9	Haematological toxicity (anemia …etc.)	1			
10	10	Hyperlactataemia/lactic acidosis	1			

91	11.9	Toxicity – other (not mentioned above)	1			
	11.99	Toxicity - unspecified	1			
90.1	12	Comorbidity		1		
92.3	13	Drug interaction		1		
92.4	13.1	Drug interaction - commencing TB/BCG treatment		1		
92.5	13.2	Drug interaction - ended TB/BCG treatment				1
96	14	Pregnancy		1		
	14.1	Pregnancy intended		1		
96.2	14.2	Pregnancy ended				1
	15	Social contra-indication		1		
Old Code	Code*	Reason for treatment discontinuation	AE	CI	FL	Other
	16.9	Contra-indication - other		1		
	16.99	Contra-indication unspecified		1		
96.1	17	MTCT regimen completed				1
94.1	18.1	Non-compliance				1
	18.2	Defaulter				1
	19	Change in treatment not due to side-effects, failure, poor adherence or contra-indication				1
92	19.1	More effective treatment available				1
92.1	19.2	Simplified treatment available				1
92.2	19.21	Treatment to complex				1
	19.3	Change in eligibility criteria (e.g. child old enough for tablets; refrigerator no longer available)				1
	19.4	Protocol change				1
97	19.51	Study treatment commenced				1
	19.52	Study treatment completed				1
	19.6	Drug not available				1

93	19.7	Structured Treatment Interruption (STI)				1
93.1	19.71	Structured Treatment Interruption (STI)-at high CD4				1
94	19.8	Patient's wish/ decision, not specified above				1
95	19.9	Physician's decision, not specified above (note overlap with standard code				1
95.1	20	Contra-indication expired				1
88	88	Death (note overlap with N/A in other lists)				1
90	90	Side effect - any of the above not mentioned	1			
99.5	95	Not ascertained				1
98	98	Other causes, not specified above				1
99	99	Unknown despite attempting ascertainment				1

*Second merge should only utilise this field. The old code has been given for lookup reference purposed for previously supplied data.

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
Name	Format	Description
OI_ED_Y	Numeric (e.g. 2001) 8885 = Ongoing	Year of end of event

	8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	
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

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	Fluconazole status

	0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	
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.

Variables to be included in additional tables

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

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

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)	Month of delivery, spontaneous abortion or termination

	95 = Not ascertained 99 = Unknown despite attempting ascertainment	
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
Name	Format	Description
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

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

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	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
Name	Format	Description
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	Site of disease if extra-pulmonary component diagnosed

	95 = Not ascertained 99 = Unknown despite attempting ascertainment	
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

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

Revised Death (Outcome) data

This table contains information about death linkage data.

Table 11 – Variables to be included in the table OUTCOME_REV

Name	Format	Description
PATIENT	Text (numerical or alphanumerical)	Unique patient identifier
COHORT	Text	Name of the cohort
REVISED OUTCOME	Numeric with codes (See List 5)	Revised outcome of death
REVISED OUTCOME _DMY	Date (for example dd/mm/yy)	Date of revised outcome
REVISION_DMY	Date (for example dd/mm/yy)	Date revision took place
MATCHABLE_FIELD	Text	Field used to match data
SOURCE	Text	Source of information update i.e. death registry

Meta-data

This table contains information about the data transfer itself.

Table 12 – 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

Appendix B: IeDEA –SA Concept Sheet for Proposed Analysis

The International Epidemiologic Databases to Evaluate AIDS Southern Africa

(IeDEA-SA)

Proposed analysis: Outcomes of infants starting ART in Southern Africa

CONCEPT SHEET FOR NEW ANALYSES

Title:	Outcomes of infants starting ART in Southern Africa
Lead author:	Mireille Porter
IeDEA senior investigator:	Brian Eley
Collaborators:	Mary-Ann Davies, James Nuttall, representative from each collaborating site
Statisticians:	Mireille Porter
Data manager:	Nicky Maxwell and Fritz Kaeser
Where will statistical analyses be done?	University of Cape Town
Has funding been requested?	Yes/No ?
If yes, please give details:	
Required variables:	
Target journal:	PIDJ/JAIDS/AIDS

Milestones:	Circulation of concept sheet: <date> Circulation of early draft paper: <date> Circulation of mature draft paper: <date> Submission to target journal: <date>
Abstract:	Advances in evidence of the benefits of early initiation of ART in infants have resulted in international treatment guidelines changes and an increase in velocity and coverage of infant ART provision. However there is limited published data on the outcomes of infants starting ART in routine care in Southern Africa. Using data merged from IeDEA sites in Southern Africa we aim to describe infant diagnostic and treatment practices at participating sites, baseline characteristics of infants starting first line ART, treatment outcomes including clinical, immunological and virological responses and identify the determinants for these outcomes.

Outline:	1. Background In 2010 a global estimate of 1.49 million infants were born to mothers living with HIV with over 1000 newly infected infants born daily.[1,2] Without ART provision it is estimated that up to 30% of HIV positive infants will die before reaching one year of age and 50% by the age of two years.[3] In addition, untreated HIV infection in infancy is associated with serious morbidity from opportunistic infections and associated organ damage including HIV encephalopathy. [4] A 2007 cohort study showed that 85% of infants would require ART by 6 months of age according to the 2006 WHO [5] immunological criteria for ART initiation in infants of CD4< 25%. In keeping with previous studies, [6, 7] this highlighted the possible clinical and immunological benefits that immediate ART initiation in infants might provide.[8] Subsequently the Children with Human Immune Deficiency Virus Early Antiretroviral Therapy Trial (CHER) done in South Africa provided clear evidence supporting early treatment of infants. HIV ART commencement before 12 weeks of age reduced mortality by 76% and disease progression by 75% in comparison to deferring ART until WHO 2006 treatment initiation criteria were met.[9] Further substudy analyses showed specific benefits of early initiation regarding short-term neurodevelopmental outcomes[10], nutrition and growth [11]. These findings resulted in changes to national and global infant ART guidelines with WHO 2010 guidelines calling for all HIV infected infants under the age of 2 years to be commenced on ART regardless of clinical or immunological factors.[3] The CHER trial showed the benefits of early ART start in a controlled trial environment. There is however limited data on the outcomes of ART initiation in infants from routine settings. Previously published studies lack power due to very small sample sizes and having been designed for other specific outcomes such as resistance. [6,7,12,13] The use of the IeDEA Southern Africa infant ART cohort will provide us the opportunity to examine the extent of implementation of WHO 2010 guidelines as well as the outcomes of infants starting ART and predictors of these outcomes. 2. Objectives and hypotheses 4. To describe infant diagnostic and treatment initiation practices at IeDEA sites in Southern Africa.

	5. To describe the baseline characteristics of infants commencing ART in IeDEA sites in Southern Africa. *6.* To describe and examine the outcomes of initiation of ART in infancy in Southern Africa and their determinants. 3. Study design 3.1 Eligibility criteria A retrospective cohort analysis of data collated from participating IeDEA Southern Africa sites • Sites included require provision of ART for infants (<1 year old) (at least 25 infants <1 year of old initiated ART since 1 January 2010) • Infants who are HIV infected (recorded PCR diagnosis or presumptive diagnosis) and ART naïve (except for PMTCT exposure) • Infants require initiation of a minimum of 3 antiretroviral drugs and a recorded date of initiation before their first birthday. A brief standardised survey at participating sites will be done to attain data on infant testing and initiation practices. 3.2 Key variables and definitions 3.2.1 Brief Description of infant HIV testing and ART initiation practices These will be determined through a brief questionnaire to site investigators. Variables will include: • Main points of entry for infants to ART services • Linkage with PMTCT services • Protocol and practice of identification of HIV positive infants • Availability of PCR diagnostic and laboratory services • Protocol and practice once identified to start including test-to-start interval • Main clinical providers of infant HIV care

- First line infant regimen used and availability

3.2.2 Infant and program characteristics at baseline initiation of ART

These will include:

- Age (Date of birth) and Gender.
- Birth weight and gestational age.
- PMTCT exposure.
- Level of care / facility.
- Measures of disease severity.
    - Clinical Disease measures
        - WHO stage
        - Stage defining illnesses
        - Opportunistic infections
- Nutritional and Growth markers

(weight and height - age and sex-adjusted z-scores

- Immunological and Virological markers

(CD4 count or percentage, Viral Load if available)

- Tuberculosis diagnosis and treatment duration
- Date of initiation ART.
- First-line regimen used.
- Primary Caregiver if available.

3.3 Outcomes

These will include:

- Probability of Death, Loss to Follow-Up(LTFU), Transfer out (TFO). LTFU will be defined as no clinic attendance for more than 6 months before the date of closure of the site database and with the date of LTFU being the date of the

last visit.

- Immunological, Virological and Growth longitudinal response characteristics for those remaining in care.
- Opportunistic Infections, emphasis on Tuberculosis diagnosis and treatment. (if available)

3.4 Statistical methods

Analysis of pooled data from infant ART sites using the agreed IeDEA Southern Africa format. For all analyses, techniques will be used that account for between cohort variation and the hierarchical structure of the data.

- Site based testing and initiation practices will be described
- Baseline characteristics of infants starting ARV's will be described using medians (IQR) and proportions as appropriate.
- Estimation of median time from ART start in an HIV-infected infant to death, LTFU and virological suppression will be done using the Kaplan-Meier method.
- Crude and adjusted associations between baseline characteristics and ART outcomes will be done using Cox Proportional Hazards models
- Immunological and growth response and their determinants will be assessed using longitudinal analysis taking into account repeated measures in individual patients.

3.5 Sample size considerations

All infants meeting eligibility criteria will be included in the study therefore no sample size calculation done.

3.6 Ethical considerations

The data to be used for this analysis are anonymised and will be obtained from individual IeDEA sites each of which has existing IRB approval for contribution of data to IeDEA collaborative analyses.

3.7 References

1. World Health Organisation (2011). "Global HIV/AIDS response epidemic update and health sector progress towards Universal Access 2011 Progress Report."

2. Penazzato M, Prendergast A , Tierney J , Cotton M F, Gibb D (2012). "Effectiveness of antiretroviral therapy in HIV-infected children under 2 years of age (Review)." Cochrane Database Systematic Review.

3. World Health Organisation (2010). "Antiretroviral Therapy For HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a public health approach. 2010 revision."

4. Puthanakit, T. and T. Bunupuradah (2010). "Early versus deferred antiretroviral therapy in children in low-income and middle-income countries." Current opinion in HIV and AIDS **5**(1): 12-17.

5. World Health Organisation (2006). "Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access Recommendations for a public health approach."

6. Luzuriaga, K., M. McManus, et al. (2004). "A Trial of Three Antiretroviral Regimens in HIV-1–Infected Children." New England Journal of Medicine **350**(24): 2471-2480.

7. Berk DR, F.-H. M., Hill DW, Albin C, Arrieta A, Bork JM, Cohan D, Nilson B, Petru A, Ruiz J, Weintrub PS, Wenman W, Maldonado YA; California Pediatric HIV Study Group. (2005). "Temporal Trends in Early Clinical Manifestations of Perinatal HIV Infection in a Population-Based Cohort." JAMA **293**(18): 2221-2231.

8. Wendy Mphatswe, N. B., Gareth Tudor-Williams, Andrew Prendergast, Christina Thobakgale, Nompumelelo Mkhwanazi, Noel McCarthy, Bruce D. Walkera, Photini Kiepiela and Philip Goulder, (2007). "High frequency of rapid immunological progression in African infants infected in the era of perinatal HIV prophylaxis." AIDS **21**(10): 1253-1261.

9. Violari A, C. M., Gibb DM, Babiker AG, Steyn J, Madhi SA, Jean- and M. J. s. Philippe P (2008). "Early antiretroviral therapy and mortality among HIV-infected infants." N Engl J Med **359**(21): 2233-2244.

10. Laughton, B., M. Cornell, et al. (2012). "Early antiretroviral

therapy improves neurodevelopmental outcomes in infants." AIDS **26**(13): 1685-1690.

11. Shiau, S., S. Arpadi, et al. (2013). "Initiation of Antiretroviral Therapy Before 6 Months of Age is Associated with Faster Growth Recovery in South African Children Perinatally Infected with Human Immunodeficiency Virus." The Journal of pediatrics.

12. Faye, A., J. Le Chenadec, et al. (2004). "Early versus deferred antiretroviral multidrug therapy in infants infected with HIV type 1." Clin Infect Dis **39**(11): 1692-1698.

13. Tukei VJ, M. M., Asiimwe AR,Migisha D,Maganda A, Bakeera-Kitaka S, Kalyesubula I, Musoke P and Kekitiinwa A (2013). "Virologic, immunologic and clinical response of infants to antireteroviral therapy in Kampala, Uganda." BMC Pediatrics **13**(42).

14. Edmonds, A., Yotebieng, M, Lusiama, J, Matumona, Y., Kitetele, F., Napravnik, S., Cole, S. R., van Rie, A. & Behets, F. 2011. The effect of highly active antiretroviral therapy on the survival of HIV-infected children in a resource-deprived setting: a cohort study. *PLoS medicine,* 8**,** e1001044.

Appendix C: Official letter of eethical approval from University of Cape Town Faculty of Health Sciences Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

08 May 2014

HREC REF: 290/2014

Dr M Davies
Public Health & Family Medicine
CIDER
Room 5.39
Falmouth Building

Dear Dr Davies

PROJECT TITLE: OUTCOMES OF INFANTS STARTING ANTIRETROVIRAL THERAPY IN SOUTHERN AFRICA (Masters Candidate – Dr M Porter)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th May 2015

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

We acknowledge that the following student, Mireille Porter will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

p TuBurgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

HREC 290/2014

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix D: Official letter of ethical approval from University of Cape Town Faculty of Health Sciences Research Ethics Committee for parent project by IeDEA (previously OASIS).

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E53-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: preaward@curie.uct..ac.za

12 April 2006

REC REF: 084/2006

Dr. A Boulle
Public Health and Family Medicine

Dear Dr. Boulle

THE OBSERVATIONAL ANTIRETROVIRAL STUDIES IN SOUTHERN AFRICA (OASIS) COLLABORATION

Thank you for submitting your study to the Research Ethics Committee for review. It is a pleasure to inform you the Ethics committee has formally approved the above mentioned study.

Please quote the REC. REF in all your correspondence.

Yours sincerely

Lesley Bleckley
DR. M BLOCKMAN
pp **CHAIRPERSON**

Appendix E: Annual Progress Report/Renewal by Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
08 MAY 2013
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	15.5.2014
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	8/5/13

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	6 May 2013		
HREC REF Number	084/2006	Current Ethics Approval was granted until	15 May 2013
Protocol title	International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) – formerly known as the Observational Antiretroviral Studies in Southern Africa – Collaboration		
Principal Investigator	Dr Mary-Ann Davies		
Department / Office Internal Mail Address	CIDER, School of Public Health & Family Medicine, 5th Floor, Falmouth Building, Anzio Rd, Observatory		
1.1 Does this protocol receive US Federal funding?		√ Yes	☐ No

2. Protocol status (tick ✓)

√	Research-related activities are ongoing
☐	Data collection is complete, data analysis only

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		N/A
Total number of records or specimens collected, reviewed or stored since last progress report		N/A
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☑ Yes	☐ No

4. Signature

Signature of PI		Date	3 May 2013
Signature of Supervisor (if PI is a student)		Date	

Appendix F: Instructions for Authors: The Pediatric Infectious Disease Journal (PIDJ)

The Pediatric Infectious Disease Journal (PIDJ)

Online Submission and Review System

SCOPE

The Pediatric Infectious Disease Journal is a peer-reviewed, multidisciplinary journal directed to physicians and other health care professionals who manage infectious diseases of childhood.

Instructions for Authors (this page)

Copyright Transfer & Disclosure (PDF)

Reprint Ordering

Permissions Requests

Reprints

Ethical/Legal Considerations

A submitted manuscript must be an original contribution not previously published (except as an abstract or preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the journal, its editors, or the publisher. All manuscripts must be submitted on-line through the journal's web site at http://pidj.edmgr.com/. See submission instructions under "Online manuscript submission."

Patient anonymity and informed consent: It is the author's responsibility to ensure that a patient's anonymity be carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. Authors should mask patients'

eyes or, if the eye area is the focus of the illustration, the patient's nose and mouth, and they should remove patients' names from figures unless written consent obtained from the patients is submitted with the manuscript.

Copyright: All authors must sign a copy of the journal's "Authorship Responsibility, Financial Disclosures, and Copyright Transfer" form and submit it at the time of manuscript submission.

Conflicts of interest: Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading “Conflicts of Interest and Source of Funding:”. For example:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker’s bureau for Organization X – the CME organizers for Company A. For the remaining authors none were declared.

In addition, each author must complete and submit the journal’s copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (www.icmje.org/update.html). The form is readily available on the manuscript submission page www.editorialmanager.com/pidj/ can be completed and submitted electronically. Please note that authors may sign the copyright transfer agreement form electronically. For

additional information about electronically signing this form, go to http://links.lww.com/ZUAT/A106.

Compliance with NIH and Other Research Funding Agency Accessibility Requirements

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism.

Permissions: Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyrighted form elsewhere, along with complete details about the source. Any permissions fees that might be required by the copyright owner are the responsibility of the authors requesting use of the borrowed material, not the responsibility of Lippincott Williams & Wilkins.

Preparation of Manuscript

Manuscripts that do not adhere to the following instructions are returned to the corresponding author for technical revision before undergoing peer review. Also, to streamline the review process, on reviewing newly submitted manuscripts, we will identify those that do not meet the mission of the journal, provide no new information or insights into management of infectious diseases or are of more local importance and better suited

for a regional journal and return them immediately to the authors to allow them to submit their work elsewhere in a timely fashion.

New Article Types

Research Reports This section comprises manuscripts on all aspects of the molecular pathogenesis and immunologic mechanisms of bacterial, viral, fungal and other infections in infants, children and adolescents. The emphasis will be on manuscripts that present data that are clinically applicable and provide a more thorough understanding of the pathophysiologic basis of infections in children and that could impact eventual treatment and prevention. The manuscripts can be formatted as original studies or brief reports and will be peer reviewed.

HIV Reports The section comprises of high-quality, high-impact original articles and brief reports of epidemiologic, clinical, translational and implementation science studies pertaining to the prevention, treatment and outcomes of HIV infection in infants, children, and adolescents.

Vaccine Reports Articles that present data from Vaccine Phase II-IV studies will appear in this section. These manuscripts receive the same peer review as articles submitted as Original Studies. The universal open access fee for all accepted manuscripts in this category is: $1500.00 US, plus an additional per-page fee with 2 options: 1) $50 per page for print and online publication; or 2) $25 per page for online only publication. All articles in this series will be available online by free access. For manuscripts in this category, authors should refer to the “Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies” published in Vaccine (2009, vol. 27; pp 2282-8) and use case definitions as developed by The Brighton Collaboration (www.brightoncollaboration.org) whenever possible.

Manuscript Submission

Online manuscript submission: All manuscripts must be submitted on-line through the new web site at http://pidj.edmgr.com/. First-time users: Please click the Register button from the menu above and enter the requested information. On successful registration, you will be sent an E-mail indicating your user name and password. Print a copy of this information for future reference. Note: If you have received an E-mail from us with an assigned user ID and password, or if you are a repeat user, do not register again. Just log in. Once you have an assigned ID and password, you do not have to re-register, even if your status changes (that is, author, reviewer, or editor). If you experience any problems, please contact Amy Newman, Journal Manager, at PIDJournal@yahoo.com, Ph 830-865-1249, Fax 214-710-2175.

Authors: Please click the log-in- button from the menu at the top of the page and on the next screen log into the system as an Author. Submit your manuscript according to the author instructions. You will be able to track the progress of your manuscript through the system. If you experience any problems, please contact Amy Newman, Journal Manager, at PIDJournal@yahoo.com, Ph 830-865-1249, Fax 214-710-2175. Requests for help and other questions will be addressed in the order received. To submit a completed manuscript, the following documents are required: Cover Letter, Title Page, Abstract, and Manuscript. Tables and figures are optional. Each portion of the manuscript must be submitted as separate documents (i.e. cover letter, title page, abstract, manuscript, tables and figures all saved as separate files). The text documents, cover letter, title page, abstract and manuscript are to be uploaded as Microsoft Word documents. Tables are to be created in Microsoft Word also. Excel tables will not load properly. All figures should be TIFF, EPS or PowerPoint files.

General format: Submit manuscripts in English. Double space all copy, including legends, footnotes, tables, and references. Use a common font such as Arial or Times Roman in size 12. Enumerate all pages of the manuscript, beginning with the Title Page as page 1, and follow in sequence to the abstract, manuscript and all other attachments. If you are unfamiliar with numbering, you can search HELP while in Microsoft Word, and it will show in detail how to number all pages.

Title page: **Title page must be submitted as a separate file**. Include on the title page: (a) complete manuscript title; (b) authors' full names, highest academic degrees, and affiliations; (c) name and address for correspondence, including Fax number, telephone number, and E-mail address; (d) address for reprints if different from that of corresponding author (indicate whether reprints are available); and (e) all sources of support, including pharmaceutical and industry support, that require acknowledgment; (f) list three to five key words for indexing; (g) an abbreviated title of 55 characters or less used for the cover of the journal; (h) a running head title of 44 characters or less including spaces used for page headings on the pages in which your article is published.

The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

Structured abstract for Original Studies and Supplement Articles: Abstracts must be submitted as a separate file. Limit the abstract to 250 words. Do not cite references in the abstract. Limit the use of abbreviations and acronyms. Use the following subheads: Background, Methods, Results, and Conclusions (others may be added as needed).

Unstructured abstract for Instructive Cases and Brief Reports: Abstract must be submitted as a separate file. Limit the abstract to 60 words. It must be factual and comprehensive.

Limit the use of abbreviations and acronyms, and avoid general statements (e.g. "the significance of the results is discussed").

Text: Organize the manuscript into four main headings, Introduction, Materials and Methods, Results, and Discussion. If a brand name is cited, supply the manufacturer's name and address (city and state/country).

Abbreviations: For a list of standard abbreviations, consult the *American Medical Association Manual of Style*, 9th edition, or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure. Abbreviations are allowed only if used three times or more in text.

References: The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in text in the order of appearance, including those references cited in tables and figure legends at the chronological citation of the tables and figures in text. Cite unpublished data, such as papers submitted but not yet accepted for publication or personal communications, in parentheses in the text. If there are more than six authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at **http://www.nlm.nih.gov/tsd/ serials/lji.html**. Sample references are given below.

Journal article

1. Trujillo M, Correa N, Olsen K, et al. Cefprozil concentrations in middle ear fluid. *Pediatr Infect Dis J*. 2000;19:268 –270.

Book chapter

2. Grose C. Bacterial myositis and pyomyositis. In: Feigin RD, Cherry JD, eds. *Textbook of*

Pediatric Infectious Diseases. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1998:704 – 708.

Entire book

3. Nelson JD, Bradley JS. *Nelson's Pocket Book of Pediatric Antimicrobial Therapy*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2000.

Proceedings

4. Harrigan PR, Dong W, Weber AE, et al. Highly mutated RT and protease [Abstract I-115]. In: 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, September 24 to 27, 1998. Washington, DC: American Society for Microbiology; 1998.

Online journals

5. Friedman SA. Preeclampsia. Obstet Gynecol. [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

World Wide Web

6. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS web site]. June 1, 1996. Available at: http://www.ama-assn.org/ special/hiv/ethics. Accessed June 26, 1997.

Figures:

A) Creating Digital Artwork

1. Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42

2. Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).

3. Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital artwork:

- Artwork should be saved as TIFF, EPS, or MS Office (DOC, PPT, XLS) files. High resolution PDF files are also acceptable.
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi. If created in an MS Office program, send the native (DOC, PPT, XLS) file.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

Remember:

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.

Figure legends: Include legends for all figures. They should be brief and specific, and they should appear on a separate manuscript page after the references. Legends should be part of the manuscript file on the disk. Use scale markers in the image for electron micrographs, and indicate the type of stain used.

Color figures: The journal accepts for publication color figures that enhance an article. Authors who submit color figures receive an estimate of the cost for color reproduction. If they decide not to pay for color reproduction, they can request that the figures be converted to black and white at no charge.

Supplemental Digital Content

Supplemental Digital Content (SDC): Authors may submit SDC via Editorial Manager to LWW journals that enhance their article's text to be considered for online posting. SDC may include standard media such as text documents, graphs, audio, video, etc. On the Attach Files page of the submission process, please select Supplemental Audio, Video, or Data for your uploaded file as the Submission Item. All SDC files should be uploaded as the author would like them presented in the final article. If an article with SDC is accepted, our production staff will create a URL with the SDC file. The URL will be placed in the call-out within the article. SDC files are not copyedited by LWW staff, they will be presented digitally as submitted. For SDC documents, any labels or legends should be included in the original SDC file when submitted. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

SDC Call-outs

Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labeled as "Supplemental Digital Content," include the sequential list

number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it will not appear elsewhere in the article.

Example:

We performed many tests on the degrees of flexibility in the elbow (see Video, Supplemental Digital Content 1, which demonstrates elbow flexibility) and found our results inconclusive.

List of Supplemental Digital Content

A listing of Supplemental Digital Content must be submitted at the end of the manuscript file. Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published.

Example:

Supplemental Digital Content 1. wmv

SDC File Requirements

All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs, authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

Tables: Create tables using the table creating and editing feature of your word processing software (e.g., Word, WordPerfect). Do not use Excel or comparable spreadsheet programs. Provide a separate document for each table. Cite tables consecutively in the text, and number them in that order. Key each on a separate sheet, and include the table title, appropriate column heads, and explanatory legends (including definitions of any abbreviation not already defined in the text). Do not embed tables within the body of the manuscript. They should be self-explanatory and should supplement, rather than duplicate, the material in the text. In each table, the genus of each genus-species must be written out at its first appearance.

Style: *Stedman's Medical Dictionary* (27th edition) and *Merriam Webster's Collegiate Dictionary* (10th edition) should be used as standard references. Refer to drugs and therapeutic agents by their accepted generic or chemical names, and do not abbreviate them. Use code numbers only when a generic name is not yet available. Capitalize the trade names of drugs and place them in parentheses after the generic names. To comply with trademark law, include the name and location (city and state/country) of the manufacturer of any drug, supply, or equipment mentioned in the manuscript. Use the metric system to express units of measure and degrees Celsius or degrees Fahrenheit consistently throughout the manuscript to express temperatures, and use SI units rather than conventional units. Abbreviate "liter" in such forms as "3 units/L" and "5 mL"; write out when used alone (10 liters; 0.5-liter gavage). See also Day RA, ed. How to Write and Publish a Scientific Paper. 5th ed. Phoenix, AZ: The Oryx Press, 1998.

Brief Reports: Papers for this section should be no longer than 5–6 double-spaced typed manuscript pages (fewer than 1500 words), 10 references and 1 figure or table. Word count does not include Title Page or Unstructured Abstract.

Letters to the Editors: Letters to the Editors should pertain to articles published within the Pediatric Infectious Disease Journal or highlight important new clinical or laboratory insights. Text should contain 500 words or fewer and less than 5 references.

Financial disclosure: In the cover letter, indicate all affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials of the research discussed in the manuscript (e.g. employment, consultancies, stock ownership). All such information will be held in confidence during the review process. Should the manuscript be accepted, the Chief Editors will discuss with the author the extent of disclosure appropriate for publication.

After Acceptance

Open access

LWW's hybrid open access option is offered to authors whose articles have been accepted for publication. With this choice, articles are made freely available online immediately upon publication. Authors may take advantage of the open access option at the point of acceptance to ensure that this choice has no influence on the peer review and acceptance process. These articles are subject to the journal's standard peer-review process and will be accepted or rejected based on their own merit.

Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. The article processing charge for *The Pediatric Infectious Disease Journal* is $3,000. The article processing charge for authors funded by the Research Councils UK (RCUK) is $3,800. The publication fee is charged on acceptance of the article and should be paid within 30 days by credit card by the author, funding agency or institution. Payment must be received in full for the article to be published open access.

Authors retain copyright: Authors retain their copyright for all articles they opt to publish open access. Authors grant LWW a license to publish the article and identify itself as the original publisher.

Creative Commons license: Articles opting for open access will be freely available to read, download and share from the time of publication. Articles are published under the terms of the Creative Commons License Attribution-NonCommerical No Derivative 3.0 which allows readers to disseminate and reuse the article, as well as share and reuse of the scientific material. It does not permit commercial exploitation or the creation of derivative works without specific permission. To view a copy of this license visit:

http://creativecommons.org/licenses/by-nc-nd/3.0.

Compliance with NIH, RCUK and other research funding agency accessibility requirements: A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW identifies to the National Library of Medicine (NLM) articles that require deposit and transmits the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism. LWW ensures that authors can fully comply with the public access requirements of major funding bodies worldwide. Additionally, all authors who choose the open access option will have their final published article deposited into PubMed Central.

RCUK funded authors can choose to publish their paper as open access with the payment of an article process charge, or opt for their accepted manuscript to be deposited (green route) into PMC with an embargo.

With both the gold and green open access options, the author will continue to sign the Copyright Transfer Agreement (CTA) as it provides the mechanism for LWW to ensure that the author is fully compliant with the requirements. After signature of the CTA, the author will then sign a License to Publish where they will then own the copyright.

It is the responsibility of the author to inform the Editorial Office and/or LWW that they have RCUK funding. LWW will not be held responsible for retroactive deposits to PMC if the author has not completed the proper forms.

FAQ for open access: http://links.lww.com/LWW-ES/A48

Page proofs and corrections: Corresponding authors receive page proofs to check the copyedited and typeset article before publication. Portable document format (PDF) files of

the typeset pages and support documents (e.g., reprint order form) are sent to the corresponding author by E-mail. Complete instructions are provided with the E-mail for downloading and printing the files and for faxing the corrected page proofs to the publisher. Those authors without an E-mail address receive traditional page proofs. It is the author's responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style stand if they do not alter the authors' meaning. Only the most critical changes to the accuracy of the content are made. Changes that are stylistic or are a reworking of previously accepted material are disallowed. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Authors may be charged for alterations to the proofs beyond those required to correct errors or to answer queries. Proofs must be checked carefully and returned within 24 to 48 hours of receipt, as requested in the cover letter accompanying the page proofs.

Reprints: Authors receive a reprint order form with the page proofs that includes reprint costs. Reprint order forms should be returned to Author Reprint Department, Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201-2436. Reprints are normally shipped 6 to 8 weeks after publication of the issue in which the item appears. Contact the Author Reprint Department, Lippincott Williams & Wilkins, 351 W. Camden Street, Baltimore, MD 21201; Fax: 410-528-4434; E-mail: reprintsgroup@lww.com with any questions.

Permissions: For permission and/or rights to use content for which the copyright holder is LWW or the society, please go to the journal's website and after clicking on the relevant article, click on the "Request Permissions" link under the "Article Tools" box that appears on the right side of the page. Alternatively, send an e-mail to customercare@copyright.com.

For Translation Rights & Licensing queries, contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: silvia.serra@wolterskluwer.com

For Special Projects and Reprints (U.S./Canada), contact Alan Moore, Director of Sales, Lippincott Williams & Wilkins, Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Phone: 215-521-8638. E-mail: alan.moore@wolterskluwer.com

For Special Projects and Reprints (non-U.S./Canada), contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0) 207 981 0600. E-mail: silvia.serra@wolterskluwer.com

Publisher's contact: Send corrected page proofs, color letters, and any other related materials to Emily Weisenreder, Emily.Weisenreder@wolterskluwer.com, 410-528-4102 (phone), 443-451-8147 (fax), or mail to Emily Weisenreder, Wolters Kluwer Health, 351 W. Camden Street, Baltimore, MD 21201.

Manuscript Checklist (before submission)

- Cover letter
- Title page (including conflicts of interest statement)
- Abstract
- Copyright Transfer & Disclosure form signed by all authors
- Manuscript with figure legend if applicable

- References double-spaced in US National Library of Medicine style
- Corresponding author and E-mail address designated (in cover letter and on title page)
- Permission to reproduce copyrighted materials or signed patient consent forms
- Acknowledgments listed for grants and technical support
- High quality print of electronic art . Tables created using table software features
- Figures created/saved as TIFF, EPS, or PowerPoint files
- At least 3 suggested reviewers

Copyright/Disclaimer Notice • Privacy Policy

Appendix G: Supplementary tables and figures for journal ready manuscript

Supplementary Table 1: Estimates from Survival Analysis (including imputed data and complete case analysis) for the outcome of mortality

Survival Analysis Estimates for outcome of mortality: Cox Regression stratified by cohort n=4945																
		Imputed Data									**Complete Data**					
		Univariate			**Multivariate***			**Model Selection ¥**			**Univariate**			**Multivariate***		
Variable		**HR**	**P value**	**95% CI**	**HR**	**P value**	**95% CI**	**HR**	**95% CI**	**VI**	**HR**	**P value**	**95% CI**	**HR**	**P value**	**95% CI**
Female gender		0.97	0.716	0.83-1.14	-	-	-	-	-	0.31	0.97	0.716	0.82-1.14	-	-	-
Age at Initiation	**0-3 months**	reference			reference			reference			reference			reference		
	3-6 months	0.90	0.417	0.71-1.15	0.87	0.268	0.68-1.11	-	-	0.22	0.90	0.417	0.71-1.15	0.92	0.619	0.66-1.29
	6-12 months	0.98	0.898	0.78-1.25	0.84	0.161	0.66-1.07	-	-	-	0.98	0.898	0.78-1.25	0.82	0.268	0.57-1.17
Severe Immune suppression (WHO 2006)		2.51	0.000	1.66-3.79	2.19	0.000	1.44-3.33	2.15	1.42-3.27	1	2.61	0.000	1.73-3.95	2.13	0.002	1.33-3.40
WHO stage 3 or 4		1.89	0.000	1.47-2.45	1.36	0.023	1.04-1.78	1.35	1.04-1.77	0.87	1.91	0.000	1.49-2.44	1.39	0.040	1.02-1.90
Severe Anaemia (DAIDS 2009)		1.57	0.003	1.18-2.10	1.34	0.062	0.98-1.82	1.29	0.82-2.05	0.79	1.56	0.003	1.17-2.10	1.37	0.070	0.97-1.92
Weight-for-Age (Z-score)	**> -2**	reference			reference			reference			reference			reference		
	-2 to -3	1.40	0.015	1.07-1.84	1.29	0.063	0.99-1.71	1.29	0.99-1.71	1	1.46	0.009	1.09-1.93	1.68	0.003	1.19-2.36
	< -3	2.55	0.000	2.04-3.19	2.23	0.000	1.78-2.80	2.22	1.78-2.79	-	2.55	0.000	2.06-3.15	2.44	0.000	1.85-3.22
ART Initiated 2010 and after		0.65	0.000	0.52-0.83	0.75	0.015	0.59-0.94	0.75	0.59-0.95	0.88	0.65	0.000	0.52-0.83	0.80	0.161	0.59-1.09

*Adjusted for age, weight-for-age category, severe immunosuppression, WHO stage 3 or 4, severe anaemia and initiation in 2010 and after

¥ Using AIC and Variable Importance (VI)

HR: Hazard Ratio

CI: Confidence Interval

Supplementary Table 2: Estimates from Survival Analysis (including imputed data and complete case analysis) for the outcomes of mortality in a subset of infants from South African sites including analysis of the associations of baseline viral load category therewith.

Survival Analysis looking at South African sites and the association of viral load with mortality: Cox Regression stratified by site n=3473																	
		Imputed Data									**Complete Data**						
		Univariate			**Multivariate***			**Model Selection¥**			**Univariate**			**Multivariate***			
Variable		**HR**	**P value**	**95% CI**	**HR**	**P value**	**95% CI**	**HR**	**95% CI**	**VI**	**HR**	**P value**	**95% CI**	**HR**	**P value**	**95% CI**	
Female gender		1.01	0.912	0.82-1.24	-	-	-	-	-	0.3	1.01	0.912	0.82-1.24	-	--	-	
Age at Initiation	**0-3 months**	reference			reference			reference			reference			reference			
	3-6 months	0.83	0.192	0.63-1.09	0.75	0.042	0.57-0.99	0.79	0.52-1.19	0.53	0.83	0.192	0.63-1.09	0.77	0.204	0.51-1.15	
	6-12 months	0.87	0.341	0.66-1.15	0.76	0.059	0.57-1.01	0.80	0.54-1.20	-	0.87	0.341	0.66-1.15	0.80	0.353	0.51-1.27	
Severe Immune suppression (WHO 2006)		2.63	0.003	1.41-4.91	2.28	0.013	1.21-4.29	2.17	1.07-4.40	0.97	2.62	0.000	1.53-4.49	2.02	0.059	0.97-4.19	
WHO stage 3 or 4		1.98	0.002	1.28-3.06	1.46	0.101	0.93-2.31	1.48	0.94-2.31	0.69	2.09	0.001	1.33-3.27	1.72	0.126	0.86-3.47	
Severe Anaemia (DAIDS 2009)		1.43	0.099	0.93-2.21	1.34	0.188	0.86-2.07	1.18	0.60-2.32	0.60	1.44	0.078	0.96-2.18	1.69	0.036	1.03-2.75	
Viral Load ≥ 1 million copies/ml		1.30	0.045	1.01-1.68	1.17	0.267	0.88-1.56	1.14	0.79-1.62	0.56	1.37	0.019	1.05-1.79	1.39	0.068	0.98-1.98	
Weight-for-Age (Z-score)	**> -2**	reference			reference			reference			reference			reference			
	-2 to -3	1.10	0.665	0.69-1.75	1.01	0.956	0.64-1.59	1.02	0.64-1.61	1	1.14	0.542	0.75-1.72	0.93	0.788	0.53-1.62	
	< -3	2.28	0.000	1.66-3.13	1.97	0.000	1.43-2.73	1.99	1.44-2.75	-	2.32	0.000	1.71-3.15	1.72	0.012	1.13-2.62	
ART Initiated 2010 and after		0.47	0.000	0.32-0.67	0.51	0.000	0.35-0.74	0.51	0.35-0.74	1	0.47	0.000	0.32-0.67	0.57	0.08	0.30-1.07	

*Adjusted for age, weight-for-age z-score category, severe immunosuppression, WHO stage 3 or 4, severe anaemia, viral load category and initiation in 2010 and after

¥ Using AIC and Variable Importance (VI)

HR: Hazard Ratio, CI: Confidence Interval

Supplementary Table 3: Estimates from Survival Analysis (including imputed and complete case analysis) for the outcomes of virological suppression in a subset of infants from South African sites with a minimum of a baseline and one other virological measure

Survival Analysis looking at South African sites and the association of viral load with time to virological suppression: Cox Regression stratified by site n=1364													
		Imputed Data						**Complete Data**					
		Univariate			**Multivariate***			**Univariate**			**Multivariate***		
Variable		**HR**	**P value**	**95% CI**	**HR**	**P value**	**95% CI**	**HR**	**P value**	**95% CI**	**HR**	**P value**	**95% CI**
Female gender		1.01	0.877	0.88-1.15	-	-	-	1.01	0.880	0.88-1.15	-	-	-
Age at Initiation	**0-3 months**	reference			reference			reference			reference		
	3-6 months	0.82	0.053	0.67-1.02	0.87	0.165	0.71-1.06	0.82	0.053	0.67-1.00	0.83	0.150	0.64-1.07
	6-12 months	0.87	0.170	0.71-1.06	0.91	0.382	0.75-1.12	0.87	0.170	0.71-1.06	0.89	0.418	0.68-1.18
Severe Immune suppression (WHO 2006)		0.88	0.236	0.72-1.08	0.97	0.793	0.79-1.19	0.88	0.214	0.72-1.08	0.99	0.976	0.76-1.30
WHO stage 3 or 4		0.78	0.011	0.64-0.94	0.84	0.105	0.69-1.04	0.77	0.013	0.63-0.95	0.71	0.010	00.55-0.92
Severe Anaemia (DAIDS 2009)		1.14	0.384	0.84-1.56	1.17	0.312	0.86-1.59	1.21	0.205	0.90-1.62	1.07	0.689	0.76-1.51
Viral Load ≥ 1 million copies/ml		0.76	0.000	0.67-0.87	0.78	0.001	0.68-0.89	0.76	0.000	0.67-0.87	0.81	0.025	0.67-0.97
Weight-for-Age (Z-score)	**> -2**	reference			reference			reference			reference		
	-2 to -3	0.85	0.126	0.69-1.05	0.88	0.233	0.71-1.09	0.94	0.611	0.74-1.19	1.01	0.956	0.73-1.39
	< -3	0.85	0.067	0.72-1.01	0.90	0.283	0.75-1.09	0.87	0.133	0.72-1.04	0.86	0.232	0.66-1.10
ART Initiated 2010 and after		1.23	0.044	1.01-1.49	1.16	0.167	0.94-1.42	1.23	0.044	1.01-1.49	1.09	0.483	0.84-1.43

*Adjusted for age, weight-for-age z-score category, severe immunosuppression, WHO stage 3 or 4, severe anaemia, viral load category and initiation in 2010 and after

HR: Hazard Ratio

CI: Confidence Interval