UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences

Virological Outcomes of HIV-Infected Children Undergoing a Single-Class Drug Substitution from Lopinavir/Ritonavir- to Efavirenz-Based Antiretroviral Treatment: a retrospective cohort study

---

KIRSTEN LEAH REICHMUTH RCHKIR001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In partial fulfilment of the requirements for the degree
Masters in Public Health (Clinical Research Track)
PPH7015W

Date of Submission:
January 2015

Supervisor:
Dr Mary-Ann Davies
Public Health and Family Medicine
University of Cape Town

Co-supervisor:
Dr James Nuttall
Paediatrics and Child Health
University of Cape Town

PART 0:

PREAMBLE

DECLARATION

I, ***Kirsten Leah Reichmuth***, 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 by myself or any other person.

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

The Harvard referencing system has been used throughout. The style for Parts A and B are based on the UCT Libraries 2014 "Harvard UCT: Handbook on citation", available at http://www.lib.uct.ac.za/sites/default/files/image_tool/images/25/resources/harvarduct-2014.pdf.

The style for Part C is based on the *Pediatric Infectious Diseases Journal* Harvard referencing guide (Appendix 2).

Signature:

Student number: RCHKIR001

Date: ***27/01/2015***

DISSERTATION SYNOPSIS

BACKGROUND:

Major advances have been made in preventing mother to child transmission of HIV (PMTCT), as well as in decreasing morbidity and mortality amongst HIV-infected infants and children. However, maintenance of excellent adherence to combination antiretroviral therapy (cART) lifelong is required to achieve optimal benefits. In addition, treatment options for children are limited by potential drug-resistance following PMTCT exposure, availability of appropriate and palatable formulations, long-term toxicity concerns and drug-interactions—notably with co-treatment for tuberculosis. Given these challenges, drug simplification strategies for children remains an important area of research.

The World Health Organisation (WHO) recommends lopinavir/ritonavir-based (LPV/r) cART as first-line for children <36 months old with the option to substitute LPV/r with a nonnucleoside reverse transcriptase inhibitor if virologic suppression is maintained. This simplification strategy is potentially cost-saving, regimen-sparing and more tolerable, with a better long-term side-effect profile. Consequently, benefits should also exist in terms of adherence. The main evidence in support of this strategy has come from trials conducted by the Nevirapine Resistance Studies (NEVEREST) group. In particular, the NEVEREST 3 trial showed that substituting LPV/r for efavirenz (EFV) in children aged 36-60 months virologically suppressed on LPV/r-based cART was protective against viral rebound and had no effect on virological failure compared with remaining on LPV/r. To our knowledge, no studies to date have examined the virologic outcomes of children changed to an EFV-based regimen after initiating a LPV/r based regimen in routine, resource-constrained settings where selection of patients as eligible for EFV substitution and subsequent monitoring practices may be less rigorous than in a trial setting.

At the International Epidemiologic Database to Evaluate AIDS—Southern Africa collaboration's (IeDEA-SA) South African sites LPV/r has been used for first-line cART in children <36 months of age irrespective of PMTCT antiretroviral exposure. At many of these sites clinicians have, at their discretion, elected to substitute LPV/r with EFV when children reach 36 months of age. This has provided the opportunity to conduct an observational study to investigate this practice in a routine-care setting – comparing outcomes in children virologically suppressed and ≥36 months old who underwent a substitution of LPV/r to EFV (substitution group) to those who remained on their initial LPV/r-based regimen (stay group).

We hypothesized that HIV-infected, cART-naive children who have had no more exposure to NVP than a single postpartum dose, who achieve and maintain virologic suppression on initial LPV/r-based cART and subsequently undergo a single drug substitution from LPV/r to EFV, do no worse virologically than comparable children who remain on LPV/r-based cART.

METHODS:

Structured literature review

The objectives of the literature review were to review the existing published research on cART regimen simplification strategies in children (with a particular focus on those substituting a PI with an NNRTI in children who had achieved virologic suppression on the PI) and to provide an understanding of how simplification strategies relate to adherence, drug resistance and adverse events, and to contextualise this within a resource-limited setting.

A Pubmed and Google Scholar search identified articles relating to PI to NNRTI substitutions in virally-suppressed children on cART in resource-constrained settings. Due to a dearth of literature examining such single drug-class substitutions, the search was expanded to other drug simplification strategies.

Retrospective cohort study

We conducted a retrospective review of cohort data prospectively collected between 2003 -2010 by the IeDEA-SA collaboration. Only data from the 8 South African sites were included. The primary aim was to compare between children in the substitution and stay group the probability of virologic non-suppression within 2 years of substitution (or an equivalent time point in the stay group).

The primary objectives were to describe the group of children who had EFV substituted for LPV/r and those who remained on LPV/r; to determine the probability undergoing a LPV/r to EFV substitution at approximately 36 months of age and identify characteristics associated with this cART change; and to compare the probability of virologic failure and time to virologic non-suppression in the stay and substitution groups after adjusting for predictors of poor virologic outcomes.

All HIV-infected children initiated on LPV/r-based cART who achieved and maintained virologic suppression by 36 months of age and with follow-up beyond 36 months of age, were included. Characteristics of children who had LPV/r substituted with EFV between 36 and 60 months of age were compared with those remaining on LPV/r using Wilcoxon rank sum, Chi-squared, and Fisher's exact tests, as appropriate.

The primary outcome was time to first HIV-RNA >400 copies/ml after 42 months of age (stay group) or after substitution (substitution group). Time to this endpoint was compared between the stay and substitution groups using Kaplan-Meier plots. The association between substitution of LPV/r with EFV and the primary outcome was assessed using Cox proportional hazard models adjusted for other predictors of virologic non-suppression. The initial description included the proportion of children lost-to-follow-up, transferred for care at another health facility, or who died after 42 months of age (stay group) or after date of substitution (substitution group).

RESULTS:

Structured literature review

The review identified very little published data on the topic. There was no routine care data apart from a few small case series. The available data did seem to support the idea of such a simplification strategy, although apart from the NEVEREST studies, all other studies only included children with no prior exposure to NNRTI for PMTCT or treatment.

Retrospective cohort study

Of 690 children included, 36 underwent substitution at a median age of 44.1 months. Groups were similar at baseline (age, anthropometry, clinical and immunological stage, HIV-RNA, cART regimen) and at 42 months/date of substitution. Thereafter, the probability of having an HIV-RNA >400 copies/ml was not significantly different between the substitution and stay groups, adjusted for other predictors of virologic rebound (adjusted HR 1.43, 95% CI 0.62; 3.30, p=0.396).

CONCLUSION:

In this observational study, children virally suppressed on LPV/r-based cART changed to EFV did no worse virologically than those remaining on LPV/r. This may be an effective simplification strategy for children not exposed to prolonged NVP prophylaxis postnatally.

ACKNOWLEGEMENTS

A very heartfelt thank you to my supervisor, Dr Mary-Ann Davies, and to my co-supervisor, Dr James Nuttall, for the guidance, patience, availability, understanding, encouragement, teaching and insight they provided. They have made this a great learning experience.

Thank you to the IeDEA-SA collaboration for allowing me to use their data.

Thank you to Prof Brian Eley for starting me on this path.

Thank you to Prof Tony Westwood, Dr Donna Stokes and the Western Cape Provincial Department of Health for allowing me a sabbatical period in which to conduct the data management and analysis.

Thank you to my partner, family and friends for ongoing support, patience, love and encouragement in helping me see it through to the end.

TABLE OF CONTENTS

PART A: PROTOCOL

PART B: LITERATURE REVIEW

PART C: JOURNAL MANUSCRIPT

PART D: APPENDICES

PART A:

PROTOCOL

1. SUMMARY

1.1. Background

The 2013 World Health Organisation (WHO) guidelines for antiretroviral treatment of children recommend a lopinavir/ritonavir (LPV/r) based combination antiretroviral therapy (cART) regimen for all children <36 months old, with the option to substitute LPV/r with a non-nucleoside reverse transcriptase inhibitor (NNRTI) in children with sustained viral suppression. Few studies describe the outcomes of this practice in routine, resource-limited settings and those that have mostly excluded children with post-partum NNRTI exposure.

Among children who initiated a LPV/r-based regimen at <36 months of age, we aim to compare those who subsequently underwent a substitution of LPV/r to EFV (substitution group) and those who remained on their initial LPV/r-based regimen (stay group) in terms of the probability of virologic non-suppression within 2 years after substitution (or an equivalent time point in the stay group).

1.2. Methods

We will do a retrospective cohort study. All HIV-infected children at International Epidemiologic Database to Evaluate AIDS - Southern Africa (IeDEA-SA) sites initiated on LPV/r-based cART at <36 months of age from 2003 to 2010, who achieve and maintain virologic suppression by 36 months of age and with follow-up beyond 36 months of age, will be included.

Characteristics of children who had LPV/r substituted with EFV between 36 and 60 months of age will be compared with those remaining on LPV/r using Wilcoxon rank sum, Chi-squared, and Fisher's exact tests, as appropriate.

The primary outcome will be time to first HIV-RNA >400 copies/ml after 42 months of age (stay group) or after substitution (substitution group). Time to this endpoint will be compared between the stay and substitution groups using Kaplan-Meier plots. The association between substitution of LPV/r with EFV and the primary outcome will be assessed using Cox proportional hazard models adjusted for other predictors of virologic non-suppression.

1.3. Anticipated outcome and benefits

We anticipate that the group of children who experience a single-class drug substitution from LPV/r to EFV will do no worse virologically than those who remain on LPV/r-based cART. However, we anticipate this may not be true for children exposed to more than a single post-partum dose of nevirapine administered for prevention of mother to child transmission of HIV.

Potential benefits include knowledge gained about whether children can safely have their antiretroviral treatment regimen simplified without increased risk of virologic nonsuppression or virologic failure.

2. ABBREVIATIONS AND DEFINITIONS 2.1. Abbreviations

3TC	lamivudine
ABC	abacavir
ARV	antiretroviral
AZT	zidovudine
cART	combination antiretroviral treatment
CHER	Children with HIV Early Antiretroviral Therapy study
D4T	stavudine
EFV	efavirenz
HIV	human immunodeficiency virus
HIV-RNA	HIV ribonucleic acid quantitative PCR measurement of viral load
IeDEA-SA	International Epidemiologic Database to Evaluate AIDS - Southern Africa
LPV/r	lopinavir/ritonavir
NEVEREST	Nevirapine Resistance Study
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
PCR	polymerase chain reaction
PI	protease inhibitor
PMTCT	prevention of mother to child transmission of HIV
WHO	World Health Organisation

2.2. Definitions

Loss-to-follow-up

No recorded visit in the 9 months prior to database closure

Stay group

Children started on LPV/r-based cART before 36 months of age whose HIV-RNA is <400 copies/ml on cART at 36 months of age and who do not undergo a drug-class change by 60 months of age

Substitution group

Children started on LPV/r-based cART before 36 months of age whose HIV-RNA is <400 copies/ml on cART at 36 months of age and who are subsequently changed to EFV-based cART as a single drug substitution where the substitution was not documented as being due to failure, toxicity or contra-indication and takes place between 36-60 months of age

Time to virologic non-suppression

Time from 42 months of age (stay group) or date of substitution (substitution group) until first HIV-RNA measure of >400 copies/ml

Values at cART initiation

The value of a specific parameter measured closest to the date of ART initiation will be considered to be the baseline value at ART initiation provided it was taken within a particular window around the date of ART initiation. The windows are within 180 days pre and 7 days post starting cART (CD4 count/percent and HIV-RNA) or within 35 days pre and 14 days post starting ART (weight and height)

Viral blip

An isolated viral load >1000 copies/mL which subsequently returns to <400 copies/mL within 24 months with no change in cART regimen

Virologic failure

Two consecutive HIV-RNA measures of >1000 copies/mL whilst on cART where the two measures are taken within one year, at least 1 month apart and at least 6 months after time of single drug substitution (substitution group) or 42 months of age (stay group)

3. INTRODUCTION

3.1. Problem Identification

Sub-Saharan Africa carries 71% of the global burden of HIV, including 88% of new childhood infections (Joint United Nations Programme on HIV/AIDS Nations [UNAIDS], 2012). Prevention of mother-to-child transmission of HIV (PMTCT) strategies are improving, with fewer children becoming vertically-infected with HIV (United Nations Children's Fund [UNICEF] 2013:6). Moreover, health outcomes of vertically-infected children have vastly improved with the use of combination antiretroviral treatment (cART), most notably if started early in infancy, as demonstrated in the CHER study (Violari et al, 2008:2241).

However, these outcomes are dependent on excellent levels of adherence to antiretrovirals, lifelong. Given the lifelong nature of the treatment, virologic failure is at some point almost inevitable, and the development of long-term side-effects is of concern (Arpadi et al, 2013). Ideally long-term regimens need to be effective, have a good safety profile and be simple so as to promote adherence. Furthermore, recommended paediatric regimens need to take into account the possibility of primary or secondary resistance to drugs used for PMTCT in infants who become infected despite such preventative measures. The greatest concern is around the non-nucleoside reverse transcriptase inhibitor (NNRTI) class; particularly nevirapine (NVP) and efavirenz (EFV).

Nevirapine has firmly established itself as the drug of choice for infants in PMTCT programmes, with good effect. Initially used as a single post-partum dose to the infant, NVP monotherapy is increasingly becoming used for ≥4 weeks as infant prophylaxis, especially in areas where exclusive breastfeeding is encouraged for infant health. In addition, as EFV-based cART becomes more widely used for pregnant and breastfeeding women both for their own health and as PMTCT, HIV-exposed infants are exposed to EFV for long durations (WHO, 2013:100-107).

Both NVP and EFV have a low genetic barrier to resistance and cross-resistance occurs between NVP and EFV. Thus, infants who fail PMTCT interventions are at risk of acquiring NNRTI-resistant HIV or developing it *de novo* (Fogel et al, 2013). Moreover, these resistance mutations have been shown to persist, which raises concern about the efficacy of NVP or EFV in cART regimens of children who have failed PMTCT (Hunt et al, 2011).

Nevirapine is no longer recommended by the World Health Organisation (WHO) for firstline use in children <36 months of age (WHO, 2010); the protease-inhibitor (PI) lopinavir/ritonavir (LPV/r) is recommended instead, irrespective of infant exposure to NVP during PMTCT. This is because LPV/r has shown better viral suppression, durability and robustness in children compared with NVP (Palumbo et al, 2010; Violari et al, 2012).

However, LPV/r formulations are expensive, have food and refrigeration requirements, require twice-daily dosing, are poorly palatable and have long-term metabolic sideeffects. Use of a protease inhibitor (PI) in the first-line may also make second-line drug choices difficult.

Consequently, the 2013 WHO “Consolidated Guidelines on the Use of Anti-Retroviral Drugs for Treating and Preventing HIV Infection” (WHO, 2013) recommend an initial LPV/r-based cART regimen for all children <36 months of age, with the option to substitute LPV/r with an NNRTI in children with sustained viral suppression (WHO, 2013:122).

This conditional recommendation attempts to provide children with a simplified longterm regimen that avoids the challenges associated with prolonged LPV/r use. This is a simplification strategy which is potentially cost-saving, regimen-sparing and more tolerable, with a better long-term side-effect profile (Vigano et al.2005). Consequently, benefits should also exist in terms of adherence. The main evidence in support of this strategy has come from the Nevirapine Resistance Studies (NEVEREST).

In 2010, the NEVEREST group published results of a randomised controlled trial in which NVP was reused as treatment in children <2 years old who had been exposed to it as a single dose during PMTCT once they had achieved virologic suppression on a LPV/rbased regimen (Coovadia et al, 2010). This showed favourable virologic outcomes for the NVP substitution arm in the short term; although by one year post-substitution a significantly greater proportion of children in the substitution arm had failed virologically. Routine viral load monitoring post-substitution was recommended as a safety mechanism to identify failures. This was also borne out in the long-term follow-up of the trial participants (Kuhn et al, 2012).

Pre-treatment genotypic resistance patterns for the trial participants were subsequently analysed in a cross-sectional study (Hunt et al, 2011). NNRTI mutations were present in 27% of pre-treatment blood samples overall, with prevalence decreasing with increasing age such that by 18 months of age all samples showed wild-type virus. In the LPV/r-toEFV substitution group a significant association was found between pre-treatment NNRTI resistance mutations and virologic failure within 52 weeks of the drug substitution. However, where NNRTI-resistant mutations were present in <25% of the viral population, they did not negatively affect the child's response to NVP once initially supressed on LPV-r-based ART (Hunt et al, 2011:1468).

These findings suggest that initial suppressive LPV/r-based cART in children exposed to perinatal NVP may "raise the threshold of the frequency of resistance mutations required to result in clinically significant differences in virologic response to therapy" (Hunt et al, 2011:1467).These findings were supported by Moorthy et al (2011), who concluded that standard HIV resistance genotyping methods should be able to identify children who could benefit from a LPV/r-to-NVP substitution.

In a second non-inferiority study (NEVEREST III) children who initiated LPV/r based regimens at <24 months old and had achieved an HIV-RNA <50copies/ml were randomised, at a median age of 4.1 years, either to continue LPV/r or have LPV/r substituted with EFV. These children had been exposed to perinatal NVP as prophylaxis. The trial was powered to look for a ≥10% difference in efficacy between the LPV/r and EFV arms. Both end-points of the trial — virologic non-suppression and virologic failure — showed EFV to be non-inferior to LPV/r in this subset of children (Coovadia et al, 2014 – unpublished).

Despite the promising preliminary results of the NEVEREST III study, there remains a concern about NNRTI resistance following the PMTCT use of NVP, particularly as very few children included in the study were exposed to more than a single dose of NVP as prolonged prophylactic use during breastfeeding was not recommended at the time that these children were infants.

3.2. Justification

To our knowledge, no studies to date have examined the virologic outcomes of children changed to an EFV-based regimen after initiating a LPV/r based regimen in routine, resource-constrained settings where selection of patients as eligible for EFV substitution and subsequent monitoring practices may be less rigorous than in a trial setting.

The IeDEA-SA collaboration includes 8 South African ART sites where LPV/r has been used for first-line cART in children <36 months of age irrespective of PMTCT antiretroviral exposure. At many of these sites clinicians have, at their discretion, elected to substitute LPV/r with EFV when children reach 36 months of age. This provides the opportunity to conduct an observational study to investigate this practice in a routinecare setting – comparing virologic outcomes in children who underwent a substitution of LPV/r to EFV (substitution group) to those who remained on their initial LPV/r-based regimen (stay group).

4. STUDY HYPOTHESIS, AIM AND OBJECTIVES

4.1. Hypothesis

The study hypothesis is that HIV-infected, cART-naive children who have had no more exposure to NVP than a single postpartum dose, who achieve and maintain virologic suppression on initial LPV/r-based cART and subsequently undergo a single drug substitution from LPV/r to EFV, do no worse virologically than comparable children who remain on LPV/rbased cART.

4.2. Aims and objectives

4.2.1. Aim

To compare virologic outcomes between children in the substitution and stay groups

4.2.2. Primary objectives

I. Describe and compare the children in the substitution and stay groups in terms of their immunological and anthropometric parameters at baseline and on cART (at 36 months of age and at either age at switch or 42 months of age, substitution and stay groups, respectively)

II. Determine the probability undergoing a LPV/r to EFV substitution at approximately 36 months old and identify patient characteristics associated with this cART change

III. Describe and compare between the stay and substitution groups the proportion of children lost-to-follow-up, transferred for care at another health facility, or who died after 42 months of age (stay group) or time of substitution (substitution group)

IV. To compare the probability of virologic non-suppression between the substitution and stay groups within the 2 years after substitution (or an equivalent time point in the stay group), after adjusting for other predictors of virologic non-suppression.

5. METHODOLOGY

5.1. Study design

This will be an observational analytical study; a retrospective review of routine care data prospectively collected between 2003 -2011 by the IeDEA-SA collaboration.

5.2. Characteristics of the study population and participating sites

Only data from eligible South African sites (2 in Kwa-Zulu Natal, 4 in the Western Cape and 2 in Gauteng) will be included. Of these sites, 7/8 are in urban settings and 7/8 are public sector clinics. Most sites provide primary level care with some providing secondary or tertiary level care. The sites serve mostly low income communities with high HIV prevalence, high levels of unemployment and inadequate housing and sanitation. The sites have previously been described in a paper by Davies et al (2009: 732).

Participants will be HIV-infected children in care at the above sites (cohorts) who meet the eligibility criteria for children as described below.

5.3. Eligibility criteria

5.3.1. Eligibility criteria for IeDEA-SA cohorts:

I. The site initiates children <36 months old on LPV/r-based cART regardless of PMTCT exposure

II. The site has changed at least one child between 36-60 months of age from LPV/r to EFV as a single drug substitution where the substitution was not documented as being due to failure, toxicity or contra-indication

5.3.2. Eligibility criteria for children

Inclusion criteria

I. Children initiating LPV/r-based cART with a backbone of 2 NRTIs at <36 months of age and remaining in care on a LPV/r based regimen until at least 36 months of age

II. Total follow-up must extend beyond 42 months of age

III. Participants must have had a viral load measured in the 12 months prior to substitution (substitution group) or within the 12 months prior to turning 36 months old (stay group)

Exclusion criteria

I. No HIV-RNA viral load monitoring data after 36 months of age
II. Children who never achieved a viral load measure of <400copies/mL on the initial LPV/r-based ART regimen
III. Children who experienced virologic failure and were switched to second-line cART prior to 36 months of age or who had defaulted by that age
IV. Children enrolled on the NEVEREST trial (which was conducted at one of the IeDEA-SA sites)

5.4. Outcomes

5.4.1. Primary outcomes

I. **Time to viral non-suppression**
Time from 42 months of age or date of substitution to first HIV RNA >400 copies/ml

II. **Viral failure**
Two consecutive HIV-RNA measures of >1000copies/ml whilst on cART, taken within one year and at least 1 month apart, the first measure being at least 6 months after date of single drug substitution or 42 months of age

5.4.2. Secondary outcomes

I. Probability of transfer out to another health facility for ongoing cART management, loss-to-follow-up or death

5.5. Data collection methods

Data was collected by participating sites in a standardised manner according to the IeDEA-SA Standard Procedure for Data Transfer, Version 2.0 / 2010 (Appendix 1) and transferred to the IeDEA Data Centre at the University of Cape Town.

Unique, anonymous patient identifiers were used, with each local site collaborator being responsible for maintaining the key linking the patient identifier with the patient.

The South African National Department of Health Guidelines 2004 (National Department of Health [NDOH], 2004) and 2010 editions (NDOH, 2010) - were used by all sites to determine when children met qualifying criteria for cART, to initiate first-line cART regimens in a standard manner, and to monitor the efficacy and safety of cART using routine clinical review and laboratory tests. Prior to 2004 local treatment protocols based on Centres for Disease Control (CDC) antiretroviral treatment guidelines were followed.

Until 2010, children <36 months old were initiated on cART if they had a WHO clinical stage 3 or 4 condition, or fulfilled the national guideline age-specific criteria for severe immune suppression. From 2010 onwards children <12 months of age were eligible for cART immediately irrespective of disease severity or CD4 count.

In terms of efficacy monitoring, South African NDOH guidelines recommended that routine HIV-RNA measurement be performed bi-annually, or 3 months after a value >1000copies/ml, with bi-annual (changing to annual in 2010) CD4 count and percentage monitoring.

Recommended safety monitoring included a full blood count, alanine transferase, total cholesterol, triglycerides and glucose performed at initiation of cART and then biannually, depending on the specific antiretroviral drugs used (NDOH; 2004:47-8). The 2010 guidelines recommended that, after the first 6 months of cART, routine annual full blood count, total cholesterol, triglycerides glucose measurement, and clinically-driven alanine transferase measurement be taken, depending on the specific antiretroviral drugs used (NDOH; 2010:31).

In practice, however, safety and efficacy monitoring and the recording of results in routine databases is unlikely to be fully completed according to the schedule recommended in the guidelines.

First-line cART regimens for children <36 months changed over time but were comprised of a backbone of 2 NRTIs (D4T or AZT or ABC plus 3TC) with either LPV/r or LPV/r plus ritonavir if on concomitant anti-tuberculosis (TB) treatment. Children on an NRTI backbone with ritonavir alone (i.e. those on TB treatment or those <6 months of age, according to the 2004 guidelines) were not included.

Drug regimens and any regimen changes were recorded, as were the reasons for any drug changes made to the initial regimen.

5.6. Sample size and power considerations

We assume the probability of undergoing a LPV/r to EFV substitution to be 10%; the probability of VL detection in the stay group to be 20%; and the probability of administrative censoring in both groups to be 10%. With these assumptions, Table 1 gives the range of total sample sizes required to in order to detect a difference in probability of VL detection between the substitute and stay groups ranging from 10 – 20% with 80% power and alpha = 0.05.

We expect approximately 1000 patients to meet our eligibility criteria; hence we will have 80% power to detect an increase in non-suppression of at least 12% (i.e. a probability of non-suppression of 32%).

Total sample size required	**Probability of VL detection* in the stay group**	**Probability of VL detection* in the substitution group**	**Hazard Ratio**
338	0.20	0.40	2.29
423	0.20	0.38	2.14
543	0.20	0.36	2.00
719	0.20	0.34	1.86
992	*0.20*	*0.32*	*1.72*
1448	0.20	0.30	1.60

* VL detection limit >400 copies/ml

Table 1. Sample size considerations

5.7. Data analysis and statistical methods

Characteristics of children at cART initiation, at 36 months of age and at 42 months of age (stay group) or date of LPV/r to EFV change (substitution group) will be described. This will be done using frequency tables and proportions for categorical data; and mean plus standard deviation (SD) or median plus interquartile range (IQR) for normally and non-normally distributed numerical data, respectively. Characteristics of children at the above time points will be compared between the stay and substitution groups using Chisquared or Fisher exact tests for categorical data and t-tests or Wilcoxon sum rank for normally and non-normally distributed numerical data, respectively.

Logistic regression methods will be used to examine associations between clinically relevant predictors of drug substitution and the probability of having undergone a LPV/r to EFV change.

Time to viral non-suppression will be measured from age 42 months (in the stay group) or date of substitution (in the substitution group) as the median age of substitution is likely to be >36 months. This is because children only become eligible for substitution from 36 months of age and will need some follow-up time during which the substitution could occur. Time from age 42months or date of substitution to viral non-suppression (Figure 1.) will be estimated using Kaplan Meier plots. The effect of substitution and relevant patient characteristics at cART initiation and at age 42 months old/date of substitution on time to virologic non-suppression will initially be explored using KaplanMeier plots stratified by each of these variables.

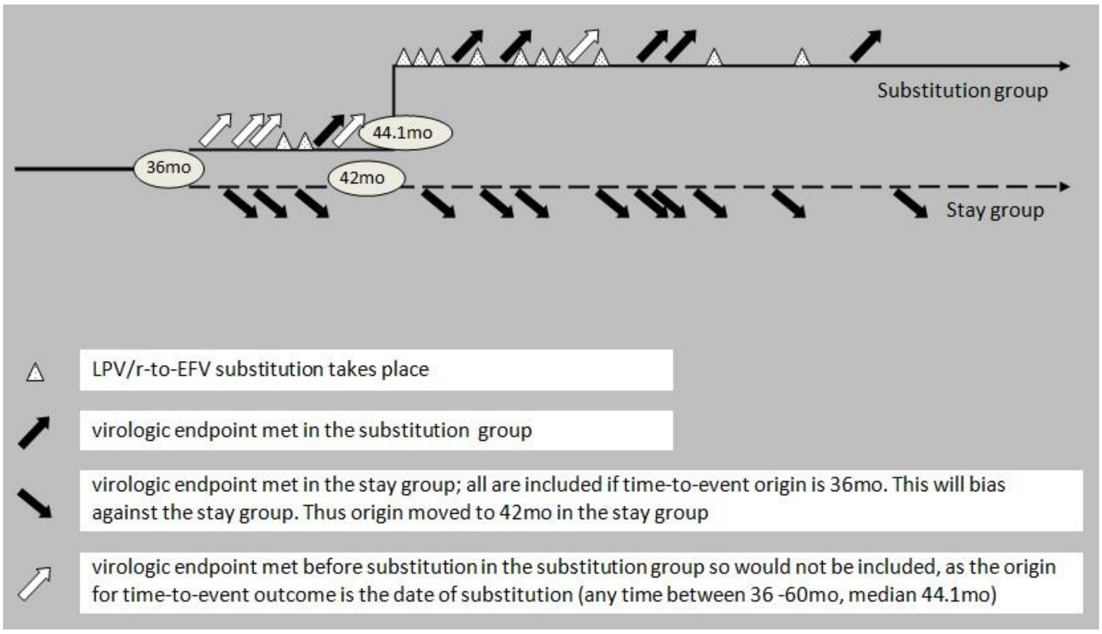

Figure 1. Schematic for chosen time points of interest

A Cox proportional hazards model, built in a manual stepwise fashion, will be used to examine the effect of changing from LPV/r to EFV after 36 months of age on the probability of subsequent viral non-suppression within 24 months, adjusted for other known predictors of virologic failure.

Potential explanatory variables to be included *a priori* are: age, clinical stage, CD4 count, HIV-RNA measurement and weight-for-age z-score (WAZ) at cART initiation; perinatal NVP exposure; CD4 count and WAZ at date closest to 42 months of age or point of substitution; and HIV-RNA blips to >400 copies/mL whilst on cART but before 36 months of age.

Variables with a p-value of <0.1 will be included in the Cox model. Models will be compared using Aikaike's information criterion (AIC) or the log-likelihood ratio test for non-nested and nested models, respectively. The final model's goodness of fit will be checked using Cox-Snell residuals. Schoenfeld residuals will be used to test whether the model meets the proportional hazards assumption. The form of the explanatory variables will be checked using Martingale residuals, whilst outlying and influential points will be identified using deviance residuals. The substitution variable will then be added to the final model, and interpreted.

A p-value of <0.05 will be considered statistically significant.

Data will be analysed using STATA®/IC 11.1 for Windows Data Analysis and Statistical Software (StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA).

6. ETHICAL CONSIDERATIONS

The data to be used for this analysis are anonymised and will be obtained from individual IeDEA sites. The University of Cape Town (South Africa) and University of Bern (Switzerland) have Institutional Review Board (IRB) approval to curate the dataset and conduct analyses; the requirement for informed consent for contribution of data to the IeDEA-SA database has been waived as only anonymised data collected as part of routine monitoring is contributed. Each site has existing IRB approval for contribution of data to IeDEA collaborative analyses (Appendix 2).

The study does not require participants to attend any additional visits, and does not require any additional blood tests or clinical monitoring to be performed; data collected is from the participants' routine care visits.

Given the retrospective, observational nature of the study it is not anticipated that the participants will incur any risks. The only potential risk is a breach of confidentiality. To protect against this risk all patient data is anonymised before transfer to the IeDEA database. The IeDEA-SA database is stored on a secure server at the University of Cape Town with user-level access controls restricted to only the named IeDEA-SA data managers. The analysis dataset will be securely stored on the student's personal computer in password-protected files. Once the analysis is complete and any manuscripts produced have been accepted for publication, the analysis dataset and files will be returned to UCT for secure archiving on the IeDEA-SA server, and all patient data on the student's computer will be permanently deleted.

Participants will not derive any individual direct benefit. However, the findings of this observational study of a routine-care treatment simplification strategy in a resourcelimited setting may benefit children on cART more broadly.

7. STUDY LOGISTICS

7.1. Budget

The National Institutes of Health provides funding for the IeDEA-SA collaboration's staff and collection and storage of data (Grant number: U01AI069924) through the National Institute of Allergy and Infectious Diseases, National Institute of Child Health and Human Development and the National Cancer Institute. No additional funding support is required and the student will not be funded to conduct the analysis.

7.2. Timeline

Year / Month	2003 -2011		2013				2014			
			Sep	**Oct**	**Nov**	**Dec**	**Jan to June**		**Jul**	**Aug**
Data collection	x	x								
Data acquisition and cleaning			x	x						
Data analysis				x	x	x				
Write-up							x	x		
Dissemination to stakeholders									x	
Submission										x

7.3. Stakeholders

Investigators at the contributing paediatric clinical sites:

- Red Cross War Memorial Children's Hospital, Cape Town: Assoc Prof Brian Eley
- Tygerberg Academic Hospital, Cape Town: Dr Helena Rabie
- Harriet Shezi Children's Clinic, Chris Hani Baragwanath Hospital, Soweto: Dr Harry Moultrie
- Médecins Sans Frontières South Africa and Khayelitsha ART Programme, Khayelitsha: Dr Vivian Cox
- Gugulethu Community Health Centre, Cape Town: Prof Robin Wood
- Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, Johannesburg: Dr Karl Technau
- Eunice Kennedy Shriver National Institute of Child Health and Human Development, Maryland, USA: Prof Lynne Mofenson

IeDEA-SA:

- School of Public Health and Family Medicine, University of Cape Town, South Africa: Dr Mary-Ann Davies
- Institute of Social and Prevention of Medicine, University of Bern, Switzerland: Prof Matthias Egger

7.4. Dissemination of study results

The results will be circulated to all of the participating IeDEA-SA sites. An abstract will be submitted to an appropriate conference and the manuscript reporting the study will be made publicly available through submission to a peer-reviewed scientific journal.

8. STUDY LIMITATIONS

Given the stringent ex- and inclusion criteria, and the fact that single-drug substitution is not a routine practice, the number of children that can be included in the analyses may be small. This is of particular concern in the substitution group.

Being a retrospective cohort study, other potential limitations could occur due to missing or incomplete data and loss to follow-up of participants. Particularly relevant would be missing information on the nature and duration of exposure to PMTCT antiretrovirals; exposure to maternal NVP or EFV via breastfeeding; missing HIV-RNA data at cART initiation; and missing data at the window around 36months of age as children may not have had a variable measured within the specified window. This may lead to a biased comparison between the stay and substitution group as we may not fully be able to adjust for confounding in the analysis. This applies both to missing data on measured as well as unmeasured confounders e.g. adherence. We will use viral blips prior to 36 months of age whilst on cART as a proxy for adherence.

As the data comes from routine practice, children may have periods with scanty data (e.g. may fall out the system then re-enter). Furthermore, with children being lost-to-followup or transferred to a different treatment site, follow-up duration may be limited and there may be under-ascertainment of both mortality and virologic failure (or nonsuppression). In terms of mortality this is not a major concern for this study as most mortality occurs early after cART initiation, whereas the eligibility criteria for this study require children to have been in care and on cART for at least 6 months. Clinicians may also be biased towards not transferring out children in whom they have elected to substitute LPV/r with EFV – either related to the reason for the substitution or to clinical anxiety about the decision. Also, children doing well on LPV/r could be more likely to be transferred out so the results in the stay group might be biased in favour of children more likely to have non-suppression.

Clinicians may have been reluctant to substitute LPV/r with EFV in children known to have had previous exposure to NVP for PMTCT; thus we may not be able to examine the effect of the substitution strategy in children with prior PMTCT exposure. In addition, during the period this data was collected the minimum standard of care for PMTCT was a single-dose of NVP to the mother in labour and to the infant immediately post-partum. Some provinces may have added AZT for 7 or 21 days to the infant regimen. Extended infant NVP prophylaxis (i.e. 6 weeks in all HIV exposed children and throughout the duration of breastfeeding; or either 4 or 12 weeks post-partum regardless of infant feeding choice, depending on risk) was not the standard of care; neither was (EFV-based) cART for all pregnant/breastfeeding women. Extended exposure to NNRTIs both ante- and postnatally is now the standard of care. Thus the findings of this study may not be generalizable to children exposed to prolonged NNRTI exposure.

9. REFERENCES

Arpadi, S., Strehlau, R., Martens, L., Patel, F., Coovadia, A., Abrams, E.J. & Kuhn, L. 2013. Metabolic Abnormalities and Body Composition of HIV-Infected Children on Lopinavir or Nevirapine-based Antiretroviral Therapy. *Arch Dis Child.* 98(4):258-64. DOI:10.1136/ archdischild-2012-302633.

Coovadia, A., Abrams, E.J., Stehlau, R., Meyers, T., Martens, T., Sherman, G. Hunt, G., Hu, C.C. et al. 2010. Reuse of Nevirapine in Exposed HIV-infected Children After Protease Inhibitorbased Viral Suppression: a randomized controlled trial. *JAMA* 304(10):1082-1090. DOI: 10.1001/jama.2010.1278

Coovadia, A., Abrams, E., Strehlau, R., Shiau, S., Pinillos, F., Martens, L., Hunt, G., Tsai, W-Y. et al. 2014. Virologic Efficacy of Efavirenz Maintenance Therapy in Nevirapine ProphylaxisExposed Children. *Proceedings on the 2014 Conference on Retroviruses and Opportunistic Infections*. 3-6 March 2014. Boston, Massachusetts, USA (Unpublished)

Davies, M.A., Keiser, O., Technau, K., Eley, B., Rabie, H., van Cutsem, G., Giddy, J., Wood, R. et al. 2009. Outcomes of the South African National Antiretroviral Treatment Programme for children: The IeDEA Southern Africa collaboration. *S Afr Med J* 99(10):730-737. Available: http://www.samj.org.za/index.php/samj/article /view/3422/2527 [Accessed: 09 July 2014]

Fogel, J.M., Mwatha, A., Richardson, P., Brown, R., Chipato, T., Alexandre, M., Moodley, D., Elbireer, A. et al. 2013. Impact of Maternal and Infant Antiretroviral Drug Regimens on Drug Resistance in HIV-infected Breastfeeding Infants. *Pediatr Infect Dis J* 32(4):e164–e169. DOI: 10.1097/INF.0b013e31827f44ee

Hunt, G.M., Coovadia, A., Abrams, E.J., Sherman, G., Meyers, T., Morris, L & Kuhn, L. 2011. HIV-1 Drug Resistance at Antiretroviral Treatment Initiation in Children Previously Exposed to Single-Dose Nevirapine. *AIDS* 25:1461-1469. DOI: 10.1097/QAD.0b013e3283492180.

Joint United Nations Programme on HIV/AIDS Nations [UNAIDS] (2012). Global summary of the AIDS epidemic. 2012 Available: http://www.unaids.org/en/media/unaids/contentassets /documents/epidemiology/2013/gr2013/201309_epi_core_en.pdf [Accessed: 11 May 2014]

Kuhn, L., Coovadia, A., Strehlau, R., Martens, L., Hu, C.C., Meyers, T., Sherman, G., Hunt, G. et al. 2012. Switching Children Previously Exposed to Nevirapine to Nevirapine-based Treatment after Initial Suppression with a Protease-Inhibitor-Based Regimen: long-term follow-up of a randomised, open-label trial. *Lancet Infect Dis* 12: 521–30. DOI:10.1016/S1473- 3099(12)70051-8

Lowenthal, E.D., Ellenberg, J.H., Machine, E., Sagdeo, B.S., Boiditswe, S., Steenhoff, A.P., Rutstein, R., Anabwani, G. et al. 2013. Association Between Efavirenz-based Compared With Nevirapine-Based Antiretroviral Regimens and Virological Failure in HIV-Infected Children. *JAMA* 309(17):1803-1809.

Moorthy, A., Kuhn, L., Coovadia, A., Meyers, T., Strehlau, R., Sherman, G., Tsai, W-Y et al. 2013. Induction Therapy with Protease-Inhibitors Modifies the Effect of Nevirapine Resistance on Virologic Response to Nevirapine-based HAART in Children. *Clinical Infectious Diseases* 52(4):514-521.

National Department of Health South Africa. 2004. National Antiretroviral Treatment Guidelines. 2004. ISBN 1-919931-69-4. Available: http://southafrica. usembassy.gov/ media/2004-doh-art-guidelines.pdf [Accessed: 12 May 2014]

National Department of Health South Africa. 2010. Guidelines for the Management of HIV in Children - 2nd Edition. Pretoria. Available: http://www.sahivsoc.org/upload/documents/Guidelines_for_Management_of_HIV_in_Children_2010.pdf [Accessed: 12 May 2014]

Moorthy, A., Kuhn, L., Coovadia, A., Meyers, T., Strehlau,R., Sherman, G., Tsai, W-Y., Chen, Y.H. et al.2011 Induction Therapy with Protease-Inhibitors Modifies the Effect of Nevirapine Resistance on Virologic Response to Nevirapine-based HAART in Children. *Clinical Infectious Diseases* 52(4):514-521. DOI:10.1093/cid/ciq161

Palumbo, P., Lindsey, J.C., Hughes, M.D., Cotton, M.F., Bobat, R., Meyers, T., BwakuraDangarembizi, M., Chi, B. et al. 2010. Antiretroviral Treatment for Children with Peripartum Nevirapine Exposure. *N Engl J Med* 363:1510-20.

United Nations Children's Fund. 2013. Towards an AIDS-Free Generation – Children and AIDS: Sixth Stocktaking Report, UNICEF, New York, 2013. Available: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20131129_stocktaking_report_children_aids_en.pdf [Accessed: 12 May 2014]

Violari, A., Cotton, M.F., Gibb, D.M., Babiker, A.G., Steyn, J., Madhi, S.A., Jean-Philippe, P. & McIntyre, J.A. 2008. Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. *N Engl J Med* 359:2233-2244.

Vigano, A., Aldrovandi, G.M., Giacomet, V, Merlo, M., Martelli, L., Beretta, S., Luraschi, P., Rombola, G. et al. 2005. Improvement in Dyslipidaemia after Switching Stavudine to Tenofovir and Replacing Protease-Inhibitors with Efavirenz in HIV-Infected Children. *Antiviral Therapy* 10:917–924.

Violari, A., Lindsey, J.C., Hughes, M.D., Mujuru, H.A., Barlow-Mosha, L., Kamthunzi, P., Chi, B.H., Cotton, M.F. et al. 2012. Nevirapine versus Ritonavir-Boosted Lopinavir for HIV-Infected Children. *N Engl J Med* 366:2380-9.

World Health Organization 2010. Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access. Recommendations for a Public Health Approach - 2010 Revision. *WHO Press*. ISBN 978 92 4 159980 1. World Health Organization (2013).

Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach - June 2013. *WHO Press*. ISBN 978 92 4 150572 7. Available: http://www.who.int /hiv/pub/guidelines/arv2013/en/ [Accessed : 12 May 2014]

PART B:

LITERATURE REVIEW

1. INTRODUCTION

Sub-Saharan Africa carries 71% of the global burden of HIV (Joint United Nations Programme on HIV/AIDS Nations [UNAIDS] 2012). An estimated 810 new childhood infections occur every day (United Nations Children's Fund [UNICEF] 2011). Fortunately, prevention of mother-to-child transmission of HIV (PMTCT) strategies are improving with vertical transmission rates, even in resource-limited settings, now as low as 2-5% (Grimwood *et al*, 2012).

Nevirapine (NVP) is firmly established as the drug of choice for infant prophylaxis in PMTCT programmes. Initially used as a single post-partum dose to the infant, NVP monotherapy is increasingly used for ≥4 weeks as infant prophylaxis, especially where exclusive breastfeeding is encouraged for infant health and mothers are not on combination antiretroviral therapy (cART). Where long-term maternal cART is instituted; i.e. World Health Organisation (WHO) Option B or B+ (WHO, 2013); breastfeeding infants face potential exposure to non-nucleoside reverse-transcriptase inhibitors (NNRTI) for extended periods via breast milk.

Early HIV testing and initiation of cART has vastly improved health outcomes in verticallyinfected children (Violari *et al*, 2008). These outcomes require excellent levels of adherence to antiretrovirals, lifelong. Given the lifelong nature of the treatment, virologic failure is at some point almost inevitable. Children are especially vulnerable as their duration of treatment is necessarily longer. Additionally, they may have either developed NNRTI resistance due to the use of infant NVP or may have inherited NNRTI resistant HIV given the use of maternal NVP or EFV for PMTCT, thereby limiting their treatment options (Hunt *et al*, 2011; Micek *et al*, 2014; Zeh *et al*, 2011; Lockman *et al*, 2007).

The WHO 2013 guidelines recommend lopinavir/ritonavir-(LPV/r) based cART for children <36 months of age, irrespective of NVP exposure (WHO, 2013:122). This is due to better viral suppression and durability of LPV/r compared with NVP (Palumbo *et al*. 2010; Violari *et al*. 2012) as well its higher genetic barrier to resistance (Tang & Shafer, 2012:e4). But LPV/r formulations are expensive, have food and refrigeration requirements, require twice-daily dosing, are poorly palatable and have unfavourable long-term metabolic sideeffects (Arpadi *et al*, 2013). Their use in the first-line makes second-line drug choices difficult. In low-income settings, treatment cost (drug, personnel and laboratory costs) and transport, storage and food requirements are also important considerations.

Drug simplification strategies, particularly those using safer drugs of comparative efficacy to those recommended in first line regimens for children, are important. Since the early 2000's researchers have attempted various cART simplification strategies, including:

- decreasing dosing intervals to once-daily
- using fixed-dose combinations (difficult given dose adjustment needed for growing children)
- using drugs that are more palatable, easier to administer or have fewer unfavourable side-effects
- planned treatment interruptions

In 2013 WHO added a conditional recommendation to substitute LPV/r with an NNRTI in children with sustained virologic suppression based on concerns of toxicity from longterm

PI use; cost, transport and availability of LPV/r syrup in areas with inadequate infrastructure; vs. the risk of NNRTI resistance following PMTCT use of NVP (WHO 2013:122). This simplification strategy is potentially cost-saving, regimen-sparing, simpler and more tolerable, with a better long-term side-effect profile (Penazzato *et al*, 2014; Vigano *et al*, 2005). Consequently benefits should exist in terms of adherence. However, there is fairly limited evidence for this recommendation. Additionally, few studies to date describe the virologic outcomes of this practice in routine, resource-constrained settings.

2. OBJECTIVES OF THE LITERATURE REVIEW

2.1. Primary objective

Review the existing published research on antiretroviral regimen simplification strategies in children, with a particular focus on those substituting a PI with an NNRTI in children who had achieved virologic suppression on the PI.

2.2. Secondary objective

Provide an understanding of how simplification strategies relate to adherence, drug resistance and adverse events; to contextualise this within a resource-limited setting, and to explore other simplification strategies.

3. SEARCH STRATEGY

An electronic literature search was performed using Pubmed® (accessed via University of Cape Town (UCT) Libraries website) and Google Scholar (via Read Cube©). A "population, intervention, comparison, outcome" (PICO) strategy was used, with exclusion terms (E), limits/restrictions (L) and secondary outcomes (2°) defined as outlined (Table 1).

All study designs were included. The search was limited to human subjects, English language text and published articles. Within these limitations the search was exhaustive as pertaining to LPV/r to EFV single-drug substitution for simplification in children on cART, but was directed with regard to the secondary objectives. Given the paucity of published literature on LPV/r to EFV single drug substitutions in children, the search was broadened (Table 1).

Article abstracts were scanned. Full-text versions articles meeting the primary and secondary objectives were downloaded via UCT Libraries (http://www.lib.uct.ac.za/). Additional articles were included by cross-referencing the articles included.

		focused search terms	broader search terms			
P	children <3yo on LPV/r-based cART	"hiv infections/drug therapy"[MeSH Terms] AND "child" NOT "adult"	"hiv infections/drug therapy"[MeSH Terms] AND "child" NOT "adult"			
I	substitution of LPV/r with EFV	"lopinavir"[MeSH Terms] AND efavirenz AND (substit* OR switch* OR simplif*)	((("lopinavir"[MeSH Terms] OR (lopinavir AND ritonavir)) OR protease inhibitor AND (efavirenz OR nevirapine OR NNRTI) AND (substit* OR switch* OR simplif*))))	n=88		
C	continue on LPV/r	-	-			
O	virological outcome	viral outcome OR virological outcome	(viral outcome OR virologic* outcome)		n=57	
2° O			adherence OR adverse event OR toxic*			
E	substitution due to failure or adverse event or toxicity	NOT toxicity OR adverse NOT failure OR virological failure OR fail*				
L	Sub-Saharan Africa	"africa south of the sahara"[MeSH Terms]	resource limit* OR resource constrain*			n=32
		n=0	n=32			

Table 1.

4. REVIEW AND INTERPRETATION OF THE LITERATURE

Of 32 articles identified, 5 met the primary objective. These are summarised in Table 2. A 6th study, the unpublished results of NEVEREST 3 which was presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston in 2014, is also included.

Three of six studies were randomised controlled trials (RCT), which rank most highly in terms of quality and validity of evidence, but are limited in not reflecting routine care and may therefore not be generalisable. One was a single-arm open label trial and one was a small case series. Case series are vulnerable to multiple biases and provide poor quality evidence, but do generate new ideas.

First author	McComsey	Vigano	Gonzalez-Tome	Coovadia (NEVEREST 1)	Kuhn (NEVEREST 2)	Coovadia (NEVEREST 3)
Date published	2003	2005	2008	2010	2012	(2015)
Study type	Multi-centre, single-arm, open label trial	Open-label RCT	Case series	Open-label RCT	Open-label RCT (long term follow-up of NEVEREST 1)	Open-label, non-inferiority RCT
Setting	USA	Italy	Spain	South Africa	South Africa	South Africa
Follow-up duration	48 weeks	96 weeks (results to week 48 published in 2005)	12 months	52 weeks	Median of 156 weeks	48 weeks
Participants	Heavily pre-treated vertically infected children >1 yo Median age 10 yr	Vertically-infected children >1yo with sustained virologic suppression on D4T, 3TC + PI Mean age 12.1 (±3.9) yr	Vertically-infected children >1yo with sustained virologic suppression on PI-based cART Median age 10yr	Vertically-infected, NVP-exposed children started on PI-based cART <24m old with sustained virologic suppression. Median age 20mo		Vertically-infected, NVP-exposed children on PI-based cART VL <50copies/ml Mean age 4.1yr
Sample size	17	28	7	195		298
Intervention	PI substituted with EFV	PI substituted with EFV and D4T substituted with TDF at baseline	PI substituted with NVP	LPV/r substituted with NVP		LPV/r substituted with EFV
Comparator	None	D4T to TDF and PI to EFV at week 24	None	LPV/r-based cART continued		LPV/r-based cART continued
Primary Outcome	Change in biochemical and clinical markers of metabolic side-effects	Change in immunologic, virologic and metabolic parameters	Change in metabolic parameters	Any viraemia (>50 copies/ml)		Rebound: any VL >50 copies/ml Failure: confirmed VL >1000 copies/ml
Secondary outcome	Viral outcome		Viral outcome	Virologic failure, biochemical, immunologic and growth markers		Biochemical, growth and immune markers and adverse events
Conclusion	PI-to-EFV substitution safe virologically More favourable side-effect profile with EFV	PI-to-EFV substitution safe virologically and immunologically	Improved lipid profile after substitution of PI with NVP	PI-to-NVP substitution virologically safe Almost all failures in the NVP group identified by 52 weeks and had pre-existing NNRTI resistance mutations Suggest monitoring of VL after substitution		Rebound: EFV group fared better Failure: EFV non-inferior to LPV/r Safe to transition from LPV/r to EFV in this patient profile
Weaknesses	Small study size NNRTI-naive Multiple biases	Small study size NNRTI-naive	Case series NNRTI-naive	Children had limited perinatal NVP exposure		Children had limited perinatal NVP exposure
Strengths	Generated new ideas re: metabolic toxicity	RCT	Generated new ideas	RCT; Sample size; prior NVP exposure		RCT; Sample size; prior NVP exposure

Table 2.

4.1. Unboosted-PI to EFV substitution with no prior NNRTI exposure:

In 2003, in America, McComsey *et al*. published a prospective multi-centre singlearm open label trial which aimed to determine whether switching from PI- to EFVbased cART would improve metabolic parameters and maintain virologic suppression (McComsey *et al*, 2003:e275-81). Seventeen vertically-infected children with an HIV-RNA viral load (VL) sustained at <400 copies/ml were included and followed-up for 48 weeks. All completed the study. The median age was 10 years and the median duration of PI-based cART was 21 months. All were heavily pretreated but none had been exposed to NNRTIs. Bar one child, the PIs used were not ritonavir-boosted as this was not yet established practice and LPV/r was not yet licensed for use. All children were switched to EFV. Minor, transient neuropsychiatric side-effects were experienced, with reported improvement in quality of life and adherence. No clinical deterioration occurred and the CD4% improved marginally (35% to 38%) by week 48. This was statistically significant (p=0.03) although of doubtful clinical significance. Anthropometric measures remained stable. At week 48, 16/17 children had a VL <50 copies/ml with one child having 61 copies/ml. Fasting triglycerides, total and low-density lipoprotein (LDL) cholesterol were all significantly reduced by week 48 in those with high baseline values, and remained within normal limits in those with normal baseline values. No change in high-density lipoprotein (HDL) cholesterol was observed, although the cholesterol to HDL ratio improved favourably. No dietary changes were made during the study period.

Study limitations included small size; possible selection bias; lack of a comparison group and blinding with potential observer or reporting bias; recall bias around adherence; measurement bias around anthropometric and laboratory measures (no detail is provided about standardisation of laboratory tests) and inter-observer bias for clinical response. Nonetheless, this study showed the PI-to-EFV switch to be virologically safe, have minimal side-effects and demonstrated an improvement in the metabolic profile in this group of heavily pre-treated children with no prior NNRTI exposure. It led to the hypothesis that nucleoside reverse transcriptase inhibitors (NRTI), not PIs, were potentially responsible for morphological changes in body fat distribution.

In 2005 an Italian study looked at changing from PI- to EFV-based cART *and* amending the NRTI backbone by substituting stavudine (D4T) –emerging as the most likely drug causing lipoatrophy - with tenofovir (TDF) to “assess the impact on immunological, virological and metabolic parameters” in vertically-infected children (Vigano *et al*, 2005:917). This prospective open-label RCT followed participants for 96 weeks. Results to 48 weeks were presented in the paper. Eligible children had to have maintained virologic suppression (VL <50 copies/ml) on a D4T, lamivudine (3TC) + PI regimen. As in the McComsey study, no child used lopinavir (LPV) and no child had used a ritonavir-boosted PI. Exclusion criteria included previous TDF or NNRTI use and a recent AIDS-defining illness. Of 28 children included, one was lost-tofollow up early in the study; 27 completed to week 48. The mean age was 12.1 (±3.9) years. Participants were randomised to change D4T to TDF and PI to EFV at baseline (Group 1, n=14) or at week 24 (Group 2, n=13). At baseline the groups were comparable in terms of age, anthropometry, CD4 count and previous ARV exposure. Both groups were reviewed clinically and had monitoring (VL and CD4) and safety (fasting lipids) bloods done at baseline and every 12 weeks until week 48. Urine analysis and serum creatinine, phosphate and bicarbonate measurement was conducted at baseline and at weeks 24 and 48. All laboratory tests were validated and standardised.

Vigano *et al*.'s findings supported McComsey's. Three children experienced minor, transient neuropsychiatric side-effects after switching to EFV. Post-switch, adherence improved by participant self-report from 80% missing a dose in the preceding 2 weeks on the PI-regimen to 17% six months after switching. CD4 counts remained stable and children remained virologically suppressed to week 48. Children in group 1 had a steady decrease in LDL cholesterol from week 12 - statistically significant at weeks 24 and 48 ($p<0.05$ and <0.01, respectively). In contrast group 2 showed no change in LDL level prior to the switch from PI to EFV at week 24. However, after children in group 2 switched, they too showed steady improvement in lipid profile (statistically significant at week 48, $p<0.01$). No renal impairment occurred in either group. Limitations included small sample size and a relatively short follow-up time. No mention was made of blinding of the statistician/data managers. A strength of the study was its design: RCT.

4.2. Unboosted-PI to NVP substitution with no prior NNRTI exposure:

In 2008 a Spanish group published a case series in which 7 HIV-infected, NNRTI-naive children with sustained virologic suppression on PI-based cART had the PI switched for NVP at the discretion of the treating clinician (Gonzalez-Tome *et al*, 2008). Reasons for the drug switch included regimen simplification (3/7), hyperlipidaemia (3/7) and lipodystrophy (1/7). The main objective was to describe the change in metabolic abnormalities following substitution but viral outcomes were also assessed. The median age of the children was 10 years and all were heavily pretreated with ARVs. Six children maintained a VL <50 copies/ml at 12 months. NVP was subjectively well tolerated.

Limitations included study design (a small case-series thus no control group), information and measurement bias (e.g. no adherence questionnaire used, advice given about diet and exercise may have affected lipid profiles but was not measured or controlled for) and selection bias. It is unclear when the study took place and how many clinicians were involved. Nonetheless, the research findings supported those of the above two studies, albeit with NVP rather than EFV.

4.3. Boosted-PI (LPV/r) to NVP substitution with prior NNRTI exposure:

In 2010, Coovadia *et al*. published an open-label RCT substituting the PI in children's first-line regimen for NVP in HIV-infected children who had been exposed to NVP as part of PMTCT; the NEVEREST[1] trial (Coovadia *et al*, 2010:1082-1090). This was the first such trial in sub-Saharan Africa; the first specifically including children with prior NVP exposure; and the largest study addressing the question of virologic safety of NNRTI use in children suppressed on PI-based cART, with 195 children undergoing randomisation.

[1] The Nevirapine Resistance Study

Recruitment took place in Johannesburg, South Africa, from April 2005 to July 2007. The median age at randomisation was 20 months. All children had been exposed to NVP[2] as part of PMTCT; all initiated PI-based cART according to South African national guidelines[3] (National Department of Health [NDOH], 2004); all had achieved and maintained virologic suppression (VL <400 copies/ml) within 12 months of starting cART.

Children were randomised to either continue with LPV/r (or RTV[3]) or switch to NVP whilst keeping the NRTI backbone unchanged. The groups did not differ significantly either before cART initiation or at randomisation in terms of median age, VL, CD4%, WHO clinical stage or anthropometric measures. Children in both groups had been on LPV/r for a median of 9 months prior to randomisation. Both groups received adherence support; VL and CD4 cell counts were quantified at weeks 4, 16, 24, 36 and 52 pre-randomization and at weeks 16, 24, 36 and 52 post-randomisation, respectively; neutrophil count and alanine transaminase (ALT) were measured at week 2 as well as at the time points above. Anthropometric data were collected throughout the study. Adherence was measured by weighing medicine returns (all syrup formulations). The primary end-point was any VL >50 copies/ml postrandomisation. Secondary end-points pertained to safety; one of which was having ≥2 VL >1000 copies/ml. Once adherence issues had been addressed, children in the switch group who met this safety end-point were put back onto LPV/r; those in the control group were changed to a second-line regimen.

Children in the switch group were significantly less likely than those in the control group to meet the primary endpoint of any VL >50 copies/ml by 52-weeks postrandomisation (probability 0.438 vs. 0.576, respectively, p=0.02). However, the switch group (n=18/96) was more likely than the control group (n=2/99) to experience the secondary endpoint of virologic failure described above (probability 0.201 vs. 0.022, respectively, p<0.001). Of the 18 children (20%) in the switch group who experienced ≥2 VL >1000 copies/ml, 3 re-suppressed on continuation of the switched regimen, 9 re-suppressed after being recommenced on LPV/r and 6 discontinued the study. Genotypic resistance testing was performed on 15/18 children; 13 had major NNRTI mutations – 10 of which were Y181C. Neither child in the control group had any major NNRTI mutations. Pre-randomisation HIV-resistance genotyping showed a strong relationship between existing major NNRTI mutations and achieving the secondary viral safety end-point (probability 0.447 in those with pre-existing mutations vs. 0.120 in those without, p=0.005). Children <12 months of age at cART initiation were more likely to have pre-randomisation genotypic resistance, but this did not translate to younger children having worse virologic outcomes. No major abnormality in ALT or neutrophil count occurred. CD4 counts improved in both groups over the study period, but the increases were likely clinically insignificant.

---

[2] The 2001 South African PMTCT guidelines allowed for a single dose of NVP to the mother in labour, and a single post-partum dose of NVP to the infant. Only in 2008 were these guidelines updated, advising ante- and intrapartum AZT to the mother and a 7 or 28 day course of infant AZT in addition to the single doses of NVP.

[3] Children > 6mo: D4T, 3TC, LPV/r; children < 6mo or on concurrent anti-tuberculosis treatment: D4T, 3TC, RTV

The NEVEREST study had many strengths: it was well-designed; adequately powered; randomisation was good; laboratory tests were specified by make and were undertaken in a single laboratory; a modified intention-to-treat analysis was performed and the statistical methods were appropriate. Additionally, both switch and control groups had minimal loss-to-follow up (5.2 and 3.0%, respectively) and only 4 children died during the study period—2 in each arm.

The trial did have some weaknesses. Although it was conducted in a low-resource setting, frequent VL testing was done and was, in fact, recommended for safety should one choose to switch LPV/r to NVP. This is not necessarily possible in many resource-constrained settings. Likewise, genotyping is difficult given the high cost. Secondly, the children recruited were born prior to 2010, and would thus have had only a single dose of NVP (sdNVP) as infant prophylaxis. In 2010 South Africa amended its PMTCT guidelines, replacing sdNVP with at least 6 weeks of NVP monotherapy for infant prophylaxis (NDOH. 2010:11-13). Lastly, length of follow-up may have been insufficient to identify all potential virologic failures.

The NEVEREST group subsequently published an article in 2012 (Kuhn *et al*, 2005:521-30) which presented results of 156 weeks of follow-up of the initial trial participants. These data showed the risk of viraemia >1000 copies/ml 156 weeks post-randomisation no longer to differ significantly between substitution and control groups (0.330 vs. 0.281, respectively). Moreover, all those in the switch group who met the criteria for failure did so within the first 52 weeks post-randomisation. In the long-term, the switch group was significantly more likely to develop a mild to moderate transaminitis, but overall NVP was well tolerated. Overall the researchers concluded that NVP-exposed children who failed PMTCT but are virologically suppressed on LPV/r-based cART can safely undergo "pre-emptive switching to a nevirapine-based regimen" (Kuhn *et al*, 2012:529) and that this "might be a valuable treatment strategy to preserve ritonavir-boosted lopinavir for future treatment while minimising adherence challenges for parents, limiting metabolic toxic effects, and reducing cost" (Kuhn *et al*, 2012:529). They advised routine VL testing preswitch and (at least) at weeks 24 and 52 post-switch.

4.4. Boosted-PI (LPV/r) to EFV substitution with prior NNRTI exposure:

EFV-based cART is associated with lower rates of virologic failure than NVP-based regimens (Lowenthal *et al*, 2013: 1086); EFV seems to be better tolerated than NVP (Shubber *et al,* 2013) and has the additional benefit of allowing a once-daily dosing regimen in combination with ABC and 3TC (Scherpbier *et al*, 2007, Musiime *et al*, 2010).

NEVEREST 3, an open-label non-inferiority RCT, examined substituting LPV/r with EFV in virologically-suppressed children 3 to 5 years old receiving LPV/r-based treatment following NVP exposure during PMTCT (Coovadia *et al*, 2014 - unpublished). Although unpublished, results from the trial were presented at CROI in March 2014. The trial had 2 primary outcomes: viral rebound (any VL >50 copies/ml) and virologic failure (any confirmed VL > 1000 copies/ml). Children were randomised to switch to EFV (n=150) or stay on LPV/r (n=148) and were followed up for 48 weeks. The groups were comparable at randomisation with regard to age, gender, mean duration on cART and the NRTI backbone used. In the LPV/r arm, 28% of children experienced viral rebound vs. 17% in the EFV arm (p=0.03). There was no difference in virologic failure between the LPV/r and EFV arms (2.0% vs. 2.6% respectively, p=0.68) by 48 weeks post-randomisation. The non-inferiority analysis favoured EFV in terms of viral rebound and found EFV to be non-inferior to LPV/r in terms of virologic failure within the specified 10% non-inferiority bound. Children in the EFV arm experienced mild, transient difficulty with sleep and experiencing nightmares. There was no significant difference between the arms of the trial in terms of CD4, growth, morbidity and mortality outcomes.

4.5. Other simplification strategies in children:

Foissac *et al*. (2011) examined once-daily LPV/r as a simplification strategy in a single centre observational study of 45 PI-experienced children in routine clinical care. This showed poorer virologic control compared to twice-daily dosing (57% vs. 74% maintaining VL <50 copies/ml, p<0.001). The KONCERT study (Lyall *et al*, 2014) was a Phase II/III randomised, open-label, multicentre, non-inferiority trial comparing once- vs. twice-daily LPV/r dosing. The median age of the 173 participants was 11yrs (IQR 3.8 – 17.7yrs). All children were virologically-suppressed on LPV/r-based cART at screening. It did not demonstrate once-daily dosing to be non-inferior to twicedaily dosing. Thus once-daily dosing of LPV/r does not seem to be a feasible simplification strategy; at least not in older children.

To address tolerability, avoidance of resistance and minimisation of side-effects, much work has recently been done on planned treatment interruptions (PTI) in children. Table 3 summarises 2 RCTs and a large prospective cohort. Treatment interruptions in the cohort study were unplanned, but it was included as being reflective of routine care. Reasons for treatment interruptions in the cohort study related to toxicity, virologic failure or drug resistance, adherence difficulties, clinical stability, palatability or tolerability issues and holiday periods. Other studies not included examined PTIs in children who were not virologically suppressed.

As seen from these studies, PTIs may have a place in reducing time on cART in carefully selected and well monitored children. The optimal duration of cART prior to PTI is still poorly understood. There is no evidence showing benefit of unstructured, unplanned treatment interruptions.

First author	Klein	Cotton	Aupiais
Published	2013	2013	2014
Study type	open, multicentre, phase II RCT	open-label RCT	multicentre, prospective cohort
Setting	Europe	South Africa	France
Duration off cART	Maximum: 48 weeks	Median: 33 weeks	Median: 12.1 months
Participants	Children virally suppressed on cART with sustained immune recovery	Asymptomatic vertically-infected children <12 weeks old not yet on cART	Children on cART
Sample size	109	377 (cART-deferred group, n=125)	483
Intervention	CD4-guided PTI of cART (n=56)	Immediate initiation of ART followed by interruption after either 40 or 96 weeks on ART (n=286)	Children >3mo who interrupted cART for >3mo (n=167)
Comparator	continuous cART (n=53)	Deferred therapy group in whom there was no subsequent interruption (n=125)	Children who remained on cART without interruption (n=316)
Primary Outcome	Composite of death, AIDS-defining condition or CD4<15%	Time to failure of first line cART (i.e. CD4<20% or symptomatic or regimen-limiting toxicity) or death Virologic control (VL not routinely measured initially)	CD4>25% and VL <500 copies/ml 3 months and 4 years after baseline
Secondary outcome	Virologic control	Time to cART restart; adverse events; virologic resistance; significant clinical events	-
Conclusion	In the PTI group CD4 counts dropped rapidly, stabilised, and returned to previous on-cART levels within 2 years of restarting cART Virologic control regained within 2 years of restarting cART PTI seems to have potential benefit	38% of children in the cART-deferred group, 25% in the ART-40W group, and 21% in the ART-96W group reached the primary endpoint PTI seems to have slightly better outcomes in infants started on cART <12 weeks old (compared with delayed continuous cART) especially given a longer duration on primary cART	Virologic control regained by 4yrs back on cART Unplanned treatment interruption associated with higher risk of severe immunodeficiency despite the reintroduction of cART (adjusted HR 3.06; 1.03-9.10, p=0.04) Not recommended
Weaknesses	Small sample size No measurement of metabolic or growth parameters		Observational study Treatment interruptions not planned No measurement of metabolic or growth parameters
Strengths	RCT Follow-up duration	RCT Sample size Clinical and adverse event data analysed	Sample size Routine care

Table 3.

5. SUMMARY

The findings by McComsey and Vigano were very useful in establishing the virologic safety of substituting a PI with EFV in NNRTI-naïve HIV-infected children. Additionally, both studies showed improved adherence on EFV, which was well tolerated. The substitution led to significant improvements in serum lipid profiles.

However, the participants in both these studies were relatively old (median age 12 and 10 yrs, respectively), were heavily pre-treated but NNRTI-naive, were not on LPV/r or ritonavir-boosted PI regimens and were recruited from high-resource settings. Thus they differ quite markedly from children in our low-resource setting, who are often NVPexposed as part of PMTCT, are usually cART-naïve when started on LPV/r-based treatment and who tend to be younger.

By the late 2000s, EFV was beginning to show superior efficacy over NVP. However, lower cost, availability of NVP-containing fixed-dose combinations and approval of NVP for use in children <3 years old made NVP the more frequently used NNRTI in low-resource settings.

The NEVEREST study opted to re-use NVP (rather than using EFV) in HIV-infected children who had been exposed to NVP as PMTCT. The median age of trial participants was much lower (20 months at randomisation). This well-designed, appropriately-powered trial had virologic outcome, not toxicity or tolerability, as the primary outcome. The results are encouraging, although they do come with the caveat of VL testing pre- and repeatedly post-substitution to ensure that children in whom the switch fails are identified promptly (and managed appropriately). HIV-resistance genotyping was further suggested in NEVEREST 2. Both tests are difficult in moderate-income-, but are likely unable to be performed in routine care in low-income settings. Additionally, inclusion of children with only sdNVP exposure limits the applicability to children currently in care who will likely have had considerably longer exposure to NVP for PMTCT. Given the high incidence of tuberculosis in Sub-Saharan Africa both NVP and LPV/r may be difficult to use; EFV would be an easier drug in such settings.

6. RECOMMENDATIONS

6.1. Current research gaps in simplifying treatment for HIV-infected children

NEVEREST 3 examined the simplification strategy of substituting LPV/r with EFV in children virologically suppressed on an initial LPV/r-based cART regimen. From this RCT the researchers concluded that the strategy was safe in children with prior NVP exposure for PMTCT and advocated consideration of such a strategy particularly in resource-limited settings.

However, as trials do not mimic practise they produce good measures of efficacy but not of effectiveness. An observational study has the potential to augment the NEVEREST 3 trial findings in a resource-limited routine clinical setting. The proposed observational cohort study should be able to provide some evidence either to support or refute the NEVEREST 3 findings. Unfortunately, like NEVEREST 3, it will be limited by the fact that participants will most likely have had only a single dose of post-partum NVP, with or without extended AZT. This will limit its generalisability to the group of young children in care born since 2010 who are most likely to have received extended NVP prophylaxis.

6.2. Potential areas of future research aimed at simplifying treatment in HIV-infected children

6.2.1. Review of infant prophylaxis in PMTCT programmes

Should WHO Option B+ (WHO. 2013:41-50) be implemented satisfactorily the need for extended infant NVP prophylaxis may become obsolete. Stratifying vertical transmission risk, as is being done in some centres, is useful in deciding on appropriate infant prophylactic regimens. The current Western Cape Department of Health PMTCT Guidelines (Western Cape Government, 2014:22-25) stratify risk, with extended NVP to low risk infants and the addition of 4 weeks of AZT to high risk infants. However, these recommendations still result in loss of the NNRTI class for treatment should the prophylaxis fail. Post-partum, sdNVP with ≥1 week of AZT (± 3TC) might be effective for low-risk infants, whilst NVP-based cART (with protection of the NVP tail) might be more effective than the current extended NVP for high-risk infants. Alternately, AZT-based regimens may be considered (Neubert *et al*, 2013). Provided the efficacy is non-inferior to extended NVP, these methods could potentially allow future use of the NNRTIs in children for whom PMTCT has failed.

6.2.2. More palatable drug formulations and simpler dosing strategies

Fixed-dose combinations are not readily available in child-suitable formulations. LPV/r syrup is poorly palatable, whilst the tablet formulation is bulky and difficult to swallow. There is promising data on the use of paediatric LPV/r mini-tab sprinkles (Musiime *et al*, 2014) which could overcome some of the challenges associated with LPV/r use.

6.2.3. Understanding resistance and sequencing of cART in children

As newer drugs are made available for use in children and as knowledge of the development of viral resistance patterns in infants and children expands, so the sequencing of ARVs may change, allowing children more options when they fail.

7. REFERENCES

Arpadi, S., Strehlau, R., Martens, L., Patel, F., Coovadia, A., Abrams, E.J. & Kuhn, L. 2013. Metabolic Abnormalities and Body Composition of HIV-Infected Children on Lopinavir or Nevirapine-based Antiretroviral Therapy. *Arch Dis Child.* 98(4):258-64. DOI:10.1136/ archdischild-2012-302633.

Aupiais, C., Faye, A., Le Chenedec, J., Rouzioux, C., Bouallag, N., Laurent, C., Blanche, S., Dollfus, C. et al. 2014. Interruption of cART in clinical practice Is associated with an increase in the long-term risk of subsequent immunosuppression in HIV-1-infected children. *Pediatr Infect Dis J* 2014;33(12):1237–1245. DOI: 10.1097/INF.0000000000000450.

Coovadia, A., Abrams, E.J., Stehlau, R., Meyers, T., Martens, T., Sherman, G. Hunt, G., Hu, C.C. et al. 2010. Reuse of Nevirapine in Exposed HIV-infected Children After Protease Inhibitor-Based Viral Suppression: a Randomized Controlled Trial. *JAMA* 304(10):1082-1090. DOI: 10.1001/jama. 2010. 1278

Coovadia, A., Abrams, E.J., Strehlau, R., Shiau, S., Martens, L., Hunt, G., Pinillos, F. et al. 2014. Virologic efficacy of efavirenz maintenance therapy in nevirapine prophylaxisexposed children. [Oral presentation] Conference on Retroviruses and Opportunistic Infections (CROI). Boston. March. (Unpublished)

Cotton, M.F., Violari, A., Otwombe, K., Panchia, R., Dobbels, E., Rabie, H., Josipovic, D., Liberty, A. et al. 2013. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. *Lancet* 382:1554-1563. http://dx.doi.org/10.1016/S0140-6736(13)61409-9

Foissac, F., Urien, S., Hirt, D., Frange, P., Chaix, ML., Treluyer, JM. & Blanche, S. 2011. Pharmacokinetics and virological efficacy after switch to once-daily lopinavir-ritonavir in treatment-experienced HIV-1-infected children. *Antimicrobial Agents and Chemotherapy* 55(9):4320-4325. DOI:10.1128/AAC.00166-11.

Gonzalez-Tome, M.I., Amador, J.T., Pena, M.J., Gomez, L.N., Conejo, P.R. & Fontelos, P.M. 2008. Outcome of Protease Inhibitor Substitution With Nevirapine in HIV-1 Infected Children. *BMC Infectious Diseases* 8:144. DOI:10.1186/1471-2334-8-144. Available: http://www.biomedcentral. com/1471-2334/8/144 [2013, January 26]

Grimwood, A., Fatti, G., Mothibi, E., Eley, B. & Jackson, D. 2012. Progress of preventing mother-to-child transmission of HIV at primary healthcare facilities and district hospitals in three South African provinces. *South African Medical Journal*, [S.l.], v. 102, n. 2, p. 8183, jan. 2012. ISSN 2078-5135. doi:10.7196/samj.5294.

Joint United Nations Programme on HIV/AIDS Nations [UNAIDS]. 2012. Global Summary of the AIDS Epidemic 2012 Available: http://www.unaids.org/en/media/unaids/contentassets/ documents/ epidemiology/2013/gr2013/201309_epi_core_en.pdf [Accessed: 2014, May 11] Klein, N., Sefe, D., Mosconi, I., Zanchetta, M., Castro, H., Jacobsen, M., Jones, H., Bernadi, S. et al. 2013. The immunological and virological consequences of planned treatment interruptions in children with HIV infection. *PLoS One* 8(10): e76582. doi:10.1371/journal.pone.0076582.

Kuhn, L., Coovadia, A., Strehlau, R., Martens, L., Hu, C.C., Meyers, T., Sherman, G., Hunt, G. et al. 2012. Switching Children Previously Exposed to Nevirapine to Nevirapine-based Treatment after Initial Suppression with a Protease-Inhibitor-Based Regimen: long-term follow-up of a randomised, open-label trial. *Lancet Infect Dis* 12: 521–30. DOI:10.1016/S1473- 3099(12)70051-8

Lockman, S., Shaipiro, R.L., Smeaton, M.S., Wester, C., Thior, I., Stevens, L., Chand, F., Makhema, J. et al. 2007. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 356(2):135-147. DOI: 10.1056/NEJM oa062876

Lyall H et al. 2014. Final results of Koncert: A randomised noninferiority trial of QD Vs BD LPV/r dosing in children. [Oral presentation74LB] *Conference on Retroviruses and Opportunistic Infections (CROI)*. Boston. March. (Unpublished) [Available at: http://www.croiwebcasts.org/console/player/22148]

McComsey, G., Bhumbra, N., Ma, J.F., Rathore, M. & Alvarez, A. 2003. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the first pediatric switch study. *Pediatrics*. 111(3):e275-e281. DOI: 10.1542/peds.111.3.e275 [2013, January 26]

Micek, M.A., Dross, S., Blano, A.J., Beck, I.A., Mathunha, L., Seidel, K, Montoya, P, Matediana, E. et al. 2014. Transmission of nevirapine-resistant HIV type 1 via breast milk to infants after single-dose nevirapine in Beira, Mozambique. *The Journal of Infectious Diseases* 210:641-645. DOI: 10.1093/infdis/jiu130

Musiime, V., Kendall, L., Bakeera-Kitaka, S., Snowden, W.B., Odongo, F, Thomason, M., Musoke, P. et al. 2010. Pharmacokinetics and Acceptability of Once- versus Twice-Daily Lamivudine and Abacavir in HIV type-1-Infected Ugandan Children in the ARROW Trial. *Antivir Ther*. 15(8):1115-24. DOI: 10.3851 /IMP1695

Musiime V, Fillekes Q, Kekitiinwa A, Kendall L, Keishanyu R, Namuddu R, Young N, Opilo W, et al. 2014. The pharmacokinetics and acceptability of lopinavir/ritonavir minitab sprinkles, tablets, and syrups in African HIV-infected children. *J Acquir Immune Def Syndr* 66(2):148-154. DOI: 10.1097/QAI.0000000000000135.

Neubert, J., Pfeffer, M., Borkhardt, A., Niehaus, T., Adams, O., Boltin, M., Reuter, S., Stannigel, H. et al. 2013. Risk adapted transmission prophylaxis to prevent vertical HIV–1 transmission: Effectiveness and safety of an abbreviated regimen of postnatal oral zidovudine. *BMC Pregnancy and Childbirth* 13(22). Available: http://www.biomedcentral.com/1471-2393/13/22

Penazzato, M., Prendergast, A.J., Muhle, L.M., Tindyebwa, D. & Abrahms, E. 2014. Optimisation of antiretroviral therapy in HIV-infected children under 3 years of age. *Cochrane Database of Systematic Reviews,* Issue 5. Art. No.: CD004772. DOI: 10.1002/14651858.CD004772.pub4.

Palumbo, P., Lindsey, J.C., Hughes, M.D., Cotton, M.F., Bobat, R., Meyers, T., BwakuraDangarembizi, M., Chi, B. et al. 2010. Antiretroviral Treatment for Children with Peripartum Nevirapine Exposure. *N Engl J Med* 363:1510-20.

Scherpbier, H.J., Bekker, V., Pajkrt, D., Jurriaans, S., Lange, J.M. & Kuijpers, T.W. 2007. Once-Daily Highly Active Antiretroviral Therapy for HIV-infected Children: Safety and Efficacy of an Efavirenz-Containing Regimen. *Pediatrics*. 119(3):e705-15

Shubber, Z., Calmy, A., Andrieux-Meyer, I., Vitoria, M., Renaud-Thery, F., Shaffer, N., Hargreaves, S. et al. 2013. Adverse Events Associated With Nevirapine and EfavirenzBased First-Line Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *AIDS.* 27(9):1403-12. DOI: 10.1097/QAD.0b013e 32835f1db0.

South Africa. National Department of Health. 2004. National Antiretroviral Treatment Guidelines. 2004. ISBN 1-919931-69-4. Available: http://southafrica. usembassy.gov/ media/2004-doh-art-guidelines.pdf [Accessed: 2014, 12 May]

South Africa. National Department of Health. 2010. Clinical Guidelines: PMTCT (Prevention of Mother-to-Child Transmission). Available: http://www.fidssa.co.za/images/PMTCT_Guidelines.pdf [Accessed: 2014, May 12]

Tang, M.W. & Shafer, R.W. 2012. HIV-1 antiretroviral resistance: scientific principles and clinical applications. Drugs 72(9):e1-e25. DOI: 0012-6667/12/0009-0001

United Nations Children's Fund. 2013. Towards an AIDS-Free Generation – Children and AIDS: Sixth Stocktaking Report, UNICEF, New York, 2013. Available: http://www. unaids.org/en/media /unaids/contentassets/documents/unaidspublication/2013/20131129_stocktaking_report_children_aids_en.pdf [Accessed: 2014, 12 May]

Vigano, A., Aldrovandi, G.M., Giacomet, V., Merlo, M., Martelli, L., Beretta, S., Luraschi, P., Rombola, G. et al. 2005. Improvement in Dyslipidaemia After Switching Stavudine to Tenofovir and Replacing Protease Inhibitors With Efavirenz in HIV-Infected Children. *Antiviral Therapy*. 10(8):917-924.

Violari, A., Cotton, M.F., Gibb, D.M., Babiker, A.G., Steyn, J., Madhi, S.A., Jean-Philippe, P. & McIntyre, J.A. 2008. Early Antiretroviral Therapy and Mortality among HIV-Infected Infants. *N Engl J Med* 359:2233-2244.

Violari, A., Lindsey, J.C., Hughes, M.D., Mujuru, H.A., Barlow-Mosha, L., Kamthunzi, P., Chi, B.H., Cotton, M.F. et al. 2012. Nevirapine versus Ritonavir-Boosted Lopinavir for HIVInfected Children.*N Engl J Med* 366:2380-9.

Western Cape Government: Health. 2014. PMTCT clinical guidelines update: June 2014.
World Health Organisation. 2010. Antiretroviral Drugs For Treating Pregnant Women and Preventing HIV Infection in Infants: Recommendations for a Public Health Approach. France: *WHO Press*. ISBN 978 92 4 159981 8. Available: http://whqlibdoc.who.int/publications/2010/ 9789241599 818_eng. pdf?ua=1 [Accessed: 2014, 12 May]

World Health Organisation. 2013. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach - June 2013. *WHO Press*. ISBN 978 92 4 150572 7. Available: http://www.who.int/hiv/pub/guidelines_/arv2013 /en/ [Accessed : 2014, 12 May]

Zeh, C., Weide, P.J., Nafisa, L., Lwamba, H.M., Okonji, J., Anyango, E., Bondo, P., Masaba, R. et al. 2011. HIV-1 drug resistance emergence among breastfeeding infants born to HIVinfected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. *PLoS Med* 8(3):e1000430. doi:10.1371/journal.pmed.1000430

Word count (excluding references and tables): 4124

PART C:

JOURNAL MANUSCRIPT

Virologic Outcomes of HIV-Infected Children Undergoing a Single-Class Drug Substitution from Lopinavir/Ritonavir- to Efavirenz-Based Antiretroviral Treatment: A retrospective cohort study.

Kirsten Leah Reichmuth

MBChB (UCT), DipHIVMan(SA)

School of Public Health, University of Cape Town

Correspondence to:

KL Reichmuth:

(🖂) New Somerset Hospital, Private Bag, Green Point, 8051

(☏) +27 21 402 6496

(💻) kirsten.reichmuth@westerncape.gov.za

Keywords:

antiretroviral, substitution, children, lopinavir, efavirenz

Abbreviated title:

"Substitution of Lopinavir With Efavirenz In Virologically Suppressed Children"

Running head title:

"Lopinavir to Efavirenz Substitution"

ABSTRACT

Background:

The WHO recommends lopinavir/ritonavir-based (LPV/r) combination antiretroviral therapy (cART) as first-line for children <36 months old with the option to substitute LPV/r with a non-nucleoside reverse transcriptase inhibitor if virologic suppression is maintained. Few studies describe outcomes of this practice in routine settings. We aimed to compare outcomes of children commencing cART with LPV/r and substituting it with efavirenz once virologically suppressed and $\geq$36 months old (substitution group) with those remaining on LPV/r (stay group).

Methods:

All HIV-infected children at IeDEA-SA sites started on LPV/r-based cART from 2003-2010 with virologic suppression at and follow-up beyond 36 months of age were included. None had >1 dose of nevirapine to prevent vertical transmission. Risk of HIV-RNA >400 copies/ml after substitution or age 42 months was compared using a Cox proportional hazards model adjusted for predictors of virologic non-suppression.

Results:

Of 690 children included, 36 underwent substitution at a median age of 44.1 months. Groups were similar at baseline (age, anthropometry, clinical and immunological stage, HIV-RNA, cART regimen) and at 42 months / date of substitution. Thereafter, the probability of having an HIV-RNA >400 copies/ml was not significantly different between the substitution and stay groups, adjusted for other predictors of virologic rebound (adjusted HR 1.43, 95% CI 0.62; 3.30, p=0.401).

Conclusions:

In this cohort, virologic outcomes of children suppressed on LPV/r-based cART and subsequently changed to efavirenz were no worse than of those remaining on LPV/r. This may be an effective simplification strategy for carefully-selected children without prolonged postnatal nevirapine exposure.

INTRODUCTION:

The World Health Organisation (WHO) recommends a lopinavir/ritonavir-based (LPV/r) combination antiretroviral therapy (cART) regimen for all HIV-infected children <36 months old irrespective of prevention of mother to child transmission of HIV (PMTCT) exposure. This is on the basis of better virologic suppression than nevirapine (NVP) (Palumbo *et al*. 2010; Violari *et al*. 2012). However, LPV/r syrup is poorly palatable, has food and refrigeration requirements, has concerning long-term metabolic side-effects and is difficult to co-administer with anti-tuberculosis (TB) treatment due to drug-drug interactions. Given these challenges, together with the need for excellent lifelong adherence to cART to achieve optimal benefits in children (Pham, 2009), drug simplification strategies for children are an important area of research. Unlike LPV/r, the non-nucleoside reverse transcriptase inhibitors (NNRTI) NVP and efavirenz (EFV) are relatively cheap, easy to administer, have no refrigeration requirements, have a reasonable long-term side effect profile and can be administered once daily. Unfortunately high-level class resistance is easy to develop (Lockman *et al*, 2007), and since NNRTIs form the basis of PMTCT, NNRTI resistance may limit treatment options in HIV-infected children who were exposed to NNRTIs antenatally, perinatally or through breastfeeding (Hunt *et al*, 2011; Micek *et al*, 2014; Zeh *et al*, 2011). Nevertheless, in 2013 the WHO added the option to substitute LPV/r with an NNRTI in children with sustained virologic suppression (WHO 2013:122). This conditional recommendation attempts to provide children with a simplified long-term regimen that avoids the challenges associated with prolonged LPV/r use. This simplification strategy is potentially cost-saving, regimen-sparing and more tolerable, with a better long-term side-effect profile (Penazzato et al, 2014; Vigano *et al*, 2005). Consequently, benefits should also exist in terms of adherence.

The main evidence in support of the LPV to NNRTI substitution strategy has come from the Nevirapine Resistance Studies (NEVEREST). The NEVEREST 1 study included children previously exposed to single-dose NVP during PMTCT who initially commenced LPV/r-based cART at <24 months of age and achieved virologic suppression within 12 months. Children were then randomized either to remain on LPV/r-based cART or to substitute LPV/r with NVP (Coovadia *et al*, 2010). NVP substitution was associated with favourable outcomes in the short term; although by one year post-substitution a significantly greater proportion of children in the substitution arm had failed virologically (confirmed viral load (VL) >1000 copies/ml). Routine VL monitoring post-substitution was recommended as a safety mechanism to identify failures timeously. This was also borne out in the long-term follow-up of the trial participants (Kuhn *et al*, 2012).

In a second non-inferiority study (NEVEREST 3) HIV-infected children exposed to perinatal NVP as prophylaxis who were initiated on LPV/r based regimens at <24 months old and had achieved virologic suppression were randomized either to continue LPV/r or have LPV/r substituted with EFV at age 3 to 5 years. The trial was powered to detect ≥10% difference in efficacy between the arms. The EFV arm showed better outcomes than the LPV/r arm in terms of viral rebound (i.e. single VL >50 copies/ml). In addition EFV was shown to be non-inferior to LPV/r in terms of virologic failure, defined as a confirmed VL >1000 copies/ml (Coovadia *et al*, 2014). Despite the promising results of NEVEREST 3, there is no published data on the outcomes of the LPV/r to EFV substitution strategy, as recommended by WHO, in routine care in resource-limited settings where children may not be monitored as rigorously as in a trial. The International epidemiologic Database to Evaluate AIDS Southern Africa (IeDEA-SA) includes 8 sites in South Africa that have used the NEVEREST 3 strategy as part of routine clinical care. We therefore aimed to compare the virologic outcomes of children aged ≥36 months who had achieved virologic suppression on a LPV/r regimen and then either remained on a LPV/r regimen (stay group) or substituted LPV/r with EFV (substitution group) in the context of routine care.

MATERIALS AND METHODS:

Study design and setting

We conducted a retrospective cohort study of HIV-infected children initiated on LPV/r-based cART before 36 months of age at 8 South African IeDEA-SA sites between 2003 and 2010. These sites have been described previously (Davies *et al*, 2009). Briefly, all but one are urban and most provide primary level care with some providing secondary or tertiary level care. South African National Department of Health guidelines (National Department of Health [NDOH], 2004; NDOH, 2010) were used by all sites to determine eligibility for cART, to initiate standard first-line cART regimens and to guide monitoring of safety and effectiveness. According to these guidelines children <36 months old qualified for cART if they had a WHO clinical stage 3 or 4 condition, or met the stated criteria for severe immune suppression. After 2010 all infants <12 months old qualified for immediate cART.

Throughout the study period a protease inhibitor-based first-line regimen was used in children <36 months of age, irrespective of NVP exposure. Between 2003-2008 children <6 months old or those receiving concurrent rifampicin-containing TB treatment were given ritonavir (RTV) alone as the protease inhibitor. This was replaced with LPV/r once >6 months old or on completion of TB treatment. After 2008 un-boosted protease inhibitors were not used; LPV/r was used in all children with additional ritonavir boosting if on concurrent rifampicin-containing TB treatment.

Until 2010 the nucleoside reverse transcriptase inhibitor (NRTI) backbone consisted of stavudine (D4T) or zidovudine (AZT) plus lamivudine (3TC).

Once children reached 36 months of age clinicians at many of the IeDEA-SA sites elected, at their discretion, to substitute LPV/r with EFV. Sites were eligible for inclusion in our analysis if they had changed at least one virologically-suppressed child from a LPV/r- to an EFV-based regimen as a single class substitution where that substitution was not due to treatment failure or toxicity.

Ethics considerations

The data used for this analysis were anonymized and were obtained from individual IeDEA-SA sites, each of which holds Institutional Review Board (IRB) approval for contributing data to the IeDEA-SA collaborative analyses. The Universities of Cape Town (South Africa) and Bern (Switzerland) have IRB approval to curate the dataset and conduct analyses.

Data collection

Data was collected by participating sites. Anonymized data was transferred to the IeDEA Data Centres using a standard procedure for data transfer. From the database we extracted demographic details (age, gender), clinical stage and PMTCT information (where available) from the initial visit; anthropometry, CD4 and VL values throughout follow-up and the start and stop dates of all antiretrovirals including reasons for any drug changes.

Definitions and outcome assessment

Substitution was defined as a single-class drug substitution, from LPV/r to EFV, in virologically-suppressed children ≥36 months old where the substitution was not due to failure or toxicity. Virologic suppression was defined as a VL <400 copies/ml in the 12 months prior to turning 36 months old (stay group) or undergoing a substitution. Children who had undergone within-class substitutions at any time point for reasons of toxicity or the introduction of newer agents (e.g. abacavir (ABC) replacing D4T or AZT in both instances) were not excluded from the analysis.

The primary outcome measure was the time to virologic non-suppression, defined as time from 42 months of age (stay group) or the date of substitution (substitution group) to first VL >400 copies/ml. Secondary outcomes included virologic failure (2 consecutive VL measures >1000 copies/ml between 30 and 365 days apart and ≥6 months after single drug substitution (substitution group) or 42 months of age (stay group)); transfer out (TFO) to another health facility for on-going management; loss to follow up (LTFU) (no visit for >270 days prior to database closure) and death.

Statistical methods

The characteristics of children at cART initiation and at either 42 months of age or at time of substitution in the stay and substitution groups were described and compared using Chi-squared or Fisher exact tests for categorical data; means, standard deviations and t-tests for normally distributed data and medians, inter-quartile ranges and Wilcoxon sum rank tests for skewed data. Logistic regression was used to examine associations between clinically relevant predictors of drug substitution and the probability of having undergone a LPV/r to EFV change. Time from age 42 months or point of substitution to virologic non-suppression was estimated using Kaplan Meier plots stratified by group and baseline clinical and immunological stage and compared using the log-rank test. We chose 42 months as the time in the stay group from which to compare outcomes with the substitution group based on a linear regression model predicting age of substitution. Since no covariates were significantly associated with substitution the intercept (44.5 months) was used as a guide. Measuring outcomes from 36 months in the stay group would introduce bias in favour of the substitution group as, in practice, children substituted many months after age 36 months. A Cox proportional hazards model was used to examine the effect of changing from LPV/r to EFV after 36 months of age on the probability virologic non-suppression within the subsequent 24 months adjusted for other known, clinically relevant predictors of virologic failure. The model was built in a manual stepwise fashion.

Potential explanatory variables for the outcome of virologic non-suppression were age, clinical stage and CD4 (absolute count and percentage) at cART initiation; perinatal NVP exposure; CD4 count and weight-for-age z-score (WAZ) at 42 months of age or at point of substitution; and viral blips whilst on cART prior to 36 months of age. A viral blip was defined as an isolated VL >1000 copies/ml which subsequently returned to <400 copies/ml at the next measurement (conducted within 24 months) with no change in cART regimen. These covariates were considered for inclusion in the final Cox model if they were associated with time to virologic failure in the univariate analysis with $p \leq 0.20$. Perinatal NVP exposure was excluded due to a paucity of PMTCT related data. Models were compared using Aikaike's information criterion (AIC) or the log-likelihood ratio test for non-nested and nested models, respectively. The substitution variable was then added to the final model and interpreted.

Data was analysed using STATA®/IC 11.1 for Windows Data Analysis and Statistical Software (StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA).

RESULTS

Description of the stay and substitution groups

Of 690 eligible children (Figure 1), 36 (5.2%) had LPV/r substituted with EFV at a median age of 44.1 months (IQR 40.9; 51.8). At initiation of cART the stay and substitution groups did not differ significantly (Table 1) in terms of median age (17.6 vs. 15.3 months), pre-cART CD4 percentage (13.9 vs. 13.0%), weight-for-age z-score (-2.34 vs. -2.56) or WHO clinical stage 3 or 4 (89.8% vs 80.8%). A cART backbone of stavudine plus lamivudine was used in >94% children in both groups. Data about PMTCT exposure was poorly captured with 73.2 vs. 66.7% of children in the stay and substitution groups, respectively, having unknown PMTCT status. However, in the substitution group no child was known to have had NVP (vs. 18/654 children in the stay group) and only 16.7% were known not to have received any PMTCT intervention (vs. 9.0% in the stay group, p=0.374). At 36 months of age—the point at which children became potentially eligible for single-class drug substitution—the groups were still comparable. Median CD4 percentage (29.3 vs. 28.6%) and weight-for-age zscores (-0.88 vs. -0.67) remained similar in the stay and substitution groups, respectively. Given the eligibility criteria, all children in both groups had a VL <400 copies/ml at 36 months of age.

At either 42 months of age or at the point of substitution—the baseline time-point for measuring the primary time-to-event outcome—the groups were not significantly different (Table 2). However, 318 (48.6%) children in the stay group experienced at least one viral blip before 36 months of age compared with 10 (27.8%) in the substitution group (p=0.015). By this time the use of abacavir had increased from 1% initially to 5.5% in each group, with stavudine use having dropped accordingly, in keeping with wider availability of abacavir for use in first-line in South Africa from 2010 onwards.

All children were followed up for at least 6 months after substitution (substitution group) or turning 42 months old (stay group). Median observation time from cART initiation to last recorded visit tended to be shorter in the stay group (52.4 vs. 60.1 months, p=0.065). However, median observation time from 42 months old in the stay group was 24.4 months (IQR 18.1; 31.7) which was similar to the median observation time from date of substitution of 25.8 months (IQR 15.1; 34.2) in the substitution group.

Factors associated with single-drug substitution

Factors considered *a priori* to be clinically relevant in deciding to institute a singledrug substitution were PMTCT exposure, immune recovery (as determined by CD4 measure) and favourable clinical response to cART (as determined by weight-for-age z-score) at 36 months of age, and whether or not the child had experienced a viral blip on cART before 36 months of age. Experiencing a viral blip (unadjusted OR 0.34, 95% CI 0.15; 0.78, adjusted OR 0.34, 95% CI 0.15 - 0.79) and an unfavourable weight-forage z-score at 36 months (adjusted OR 1.34 per 1 z-score increase, 95% CI 0.96; 1.80) were associated with not undergoing a single-drug substitution. In this cohort PMTCT exposure was excluded due to paucity of data whilst CD4 measure (percentage or absolute count) at the time of eligibility for substitution was not significantly associated with undergoing a substitution.

Outcomes after substitution

Three children (0.43%) died after 42 months of age; all in the stay group. More children in the stay group were transferred to other facilities for on-going care (42.5% vs. 25.0% in the substitution group (p=0.039)). The proportion of children lost to follow-up was twice as high in the substitution group, although this was not statistically significant (11.1 vs. 5.4%, p=0.139).

Overall 66 (9.6%) children experienced virologic failure; 64 (9.8%) in the stay and 2 (5.6%) in the substitution group (p=0.565). However, of the children who had one VL >1000 copies/ml only 67.5% vs. 67.7% in the stay and substitution groups had a repeat VL measure before the end of follow-up.

The incidence rate ratio of the time-to-event endpoint of first VL >400 copies/ml was 1.03 (95% CI 0.43 to 2.08) in the substitution relative to the stay group. The following clinically relevant variables were associated with time to first VL >400 copies/ml after 42 months of age/substitution: duration on cART prior to 42mo /substitution (adjusted HR 0.96 per extra month on cART, 95% CI 0.93; 0.98, p=0.002), weight-for-age zscore at initiation of cART (adjusted HR 0.87 per 1 z-score increase, 95% CI 0.78; 0.98, p=0.022), and having experienced at least one viral blip before 36 months of age (adjusted HR 2.26, 95% CI 1.52; 3.36, p<0.001). Having undergone a LPV/r to EFV substitution was not associated with time to first VL >400 copies/ml after 42months of age/ post-substitution (unadjusted HR 1.02, 95% CI 0.44; 2.32) even when adjusted for the variables above (adjusted HR 1.43, 95% CI 0.62; 3.30, p=0.401) (Table 4).

Of the 36 children who were switched to EFV, 7 (19.4%) were changed back to LPV/r within a median period of 5.5 (IQR 2.7 – 6.6) months. There was no reason recorded for reinstitution of LPV/r in 4 of the children, while 2 were recorded as having virologic failure and one had a VL of 12 000 copies/ml after 2 months on EFV. Four of these children had experienced at least one blip prior to 36 months of age; whilst none of the children successfully remaining on the switched regimen had experienced any such blips. In 5/7 children the return to LPV/r was virologically successful, one child had no subsequent VL measurement whilst on the study and cART was stopped in one child due to non-adherence. Six of the seven children came from the same site (supplementary material: Table 5).

DISCUSSION

In our cohort study, conducted in the context of routine, public-sector care in South Africa, we found no difference in the probability of virologic non-suppression between children ≥36 months of age who substituted LPV/r with EFV compared to those who remained on a LPV/r-based cART regimen. This finding concurs with the results of the NEVERST 3 trial, suggesting generalizability beyond the clinical trial setting. We also found that children who had experienced viral blips were both less likely to undergo substitution and more likely to experience virologic non-suppression irrespective of whether they were substituted or not.

In this cohort, 496 (87.3%) children were severely immune suppressed prior to cART initiation, 540 (89.4%) of those with a recorded baseline clinical stage had symptomatic HIV infection with 320 (58.2%) children being either severely (WAZ ≤-3) or moderately (WAZ ≤-2) underweight for age (Table 1). By 36 months of age the children had responded well to cART, with CD4% increasing and WAZ improving to within near-normal values (median WAZ -0.82; IQR -1.60 to -0.08). This excellent response in growth is likely due to the young age of the cohort (McGrath *et al*, 2011). Moreover, since nutritional status improves with control of viral replication in children, an improved WAZ likely reflects both good adherence and improved overall health (Tukei *et al*, 2013). This would probably explain why, at 36 months of age, a more favourable WAZ was positively associated with the probability of undergoing a LPV/r to EFV substitution. Conversely, viral blips imply periods of sub-optimal or variable adherence to cART. In the study, children who experienced viral blips prior to 36 months of age were less likely than those who hadn't to undergo single-drug substitution. Thus, clinicians seem to have chosen children with a good clinical response and a record of good adherence as candidates for simplification. This is likely to have introduced selection bias in favour of the substitution group. The finding that 7 (19.4%) children were switched back to LPV/r within a very short period after the substitution is concerning. Given the short time period one could assume that sideeffects or tolerability may have played a role. It is also notable that more than half (4 of 7) the children who were changed back to LPV/r after substitution had experienced viral blips prior to substitution, suggesting that substitution may not be an optimal strategy in patients with poor adherence to their primary regimen. Notably, the 2 children changed back to LPV/r due to documented failure after the substitution both had evidence of variable adherence on their initial regimen, with viral blips. Reassuringly, however, 5 of the 7 children (71%) re-suppressed on LPV/r.

A child's exposure to NNRTIs during the peripartum/neonatal period may be a critical factor in deciding about simplifying to an EFV-based regimen, given the low genetic barrier to high level NVP resistance and the cross-resistance that occurs between NVP and EFV. A limitation of this study was the paucity of accurate PMTCT data. Overall 72.9% of children had PMTCT history recorded as being unknown, 9.4% were known not to have received any PMTCT intervention, whilst only 2.6% had the actual drugs and duration of PMTCT regimens recorded. We were therefore unable to determine whether PMTCT exposure influenced clinicians' decision to substitute therapy or had an impact on virologic non-suppression after substitution/42 months of age. Although this is a weakness of the study, it probably reflects the reality clinicians often face, i.e. limited or inaccurate history regarding PMTCT, although with increasing PMTCT coverage and cART initiation at younger ages following the CHER trial findings (Violari et al, 2008) and WHO 2010 guidelines (WHO, 2010), knowledge of PMTCT exposure is likely to be better known and recorded. It is important to remember that throughout the study period infants would not have received more than a single dose of NVP post-partum, which may have been given with a 7 or 28 day course of AZT, as per the prevailing PMTCT guidelines. Furthermore, EFV-based cART for all pregnant mothers from 14 weeks of gestation to (at least) the end of breastfeeding was also not practised during the study period. This study's results would thus not be applicable to current children; except those known to have had no PMTCT exposure.

Other limitations included paucity of data around adherence (VL blips were considered a proxy for poor adherence), social factors, other comorbidities and side-effects. NEVEREST 3 reported a high but transient incidence of neuropsychiatric symptoms after substitution to EFV. Lack of data on adverse events precluded us from fully assessing the safety of the strategy.

It seems clinically significant that LTFU was twice as high in the substitution group, but the reasons are unclear. Likewise, the difference in TFO of patients between groups may have introduced selection bias. However, the groups were followed up for a relatively equivalent duration post-substitution/42 months of age. This is reassuring as the finding of no significant difference in time to viral failure between the groups is unlikely to be due to differential follow-up time. Sample size was smaller than anticipated in our initial sample size and power calculations, thus increasing the chance of a type 2 error. The number of children undergoing a LPV/r to EFV substitution was also small, thus uncertainty exists around our finding of no significant difference in virologic outcomes between the groups.

CONCLUSION

In this cohort of South African HIV-infected children on LPV/r-based cART in a routine care setting, substitution of LPV/r with EFV after 36 months of age in those who achieved and maintained virologic suppression was not associated with an adverse virologic outcome, supporting findings of the NEVEREST III randomised-controlled trial. However, this cohort was not exposed to more than a single postpartum dose of NVP as infant prophylaxis, hence this treatment simplification strategy may not be effective in children who have had prolonged NVP as infant prophylaxis.

REFERENCES

Coovadia A, Abrams EJ, Stehlau R, et al. Reuse of nevirapine in exposed HIVinfected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA* 2010;304(10):1082-1090. DOI: 10.1001/jama. 2010.1278

Coovadia A, Abrams EJ, Strehlau R et al. Virologic Efficacy of Efavirenz Maintenance Therapy in Nevirapine Prophylaxis-Exposed Children. In: Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, 03-06 March 2014.

Davies MA, Keiser O, Technau K, et al. Outcomes of the South African National Antiretroviral Treatment Programme for children: The IeDEA Southern Africa collaboration. *S Afr Med J 2009;*99(10):730-737. Available: http://www.samj.org.za/index.php/samj/article /view/3422/2527 [Accessed: 09 July 2014]

Hunt GM, Coovadia A, Abrams EJ, et al. HIV-1 drug resistance at antiretroviral treatment initiation in children previously exposed to single-dose nevirapine. *AIDS* 2011;25(12):1461-1469. DOI:10.1097/QAD.0b013e3283492180.

Kuhn L, Coovadia A, Strehlau R, et al. Switching children previously exposed to nevirapine to nevirapine-based treatment after initial suppression with a proteaseinhibitor-based regimen: long-term follow-up of a randomised, open-label trial. *Lancet Infect Dis* 2012 ;12: 521–30. DOI:10.1016/S1473- 3099(12)70051-8

Lockman S, Shaipiro RL, Smeaton MS, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 2007;356(2):135-147. DOI: 10.1056/NEJM oa062876

McGrath CJ, Chung MH, Richardson BA, et al. Younger age at HAART initiation is associated with more rapid growth reconstitution. *AIDS* 2011;25(3):345-355. DOI: 10.1097/QAD.0b013e 32834171db

Micek MA, Dross S, Blano AJ, et al. Transmission of nevirapine-resistant HIV type 1 via breast milk to infants after single-dose nevirapine in Beira, Mozambique. *The Journal of Infectious Diseases* 2014;210:641-645. DOI: 10.1093/infdis/jiu130

Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med* 2010;363:1510-20.

Penazzato, M, Prendergast, AJ, Muhle, LM, Tindyebwa, D & Abrahms, E. 2014. Optimisation of antiretroviral therapy in HIV-infected children under 3 years of age. *Cochrane Database of Systematic Reviews*, Issue 5. Art. No.: CD004772. DOI: 10.1002/14651858.CD004772.pub4.

Pham PA. Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression. *AIDS Patient Care and STDs* 2009;23(10):803-807. DOI: 10.1089 =apc.2008.0269

South Africa. National Department of Health. 2004. National antiretroviral treatment guidelines. 2004. ISBN 1-919931-69-4. Available: http://southafrica. usembassy.gov/ media/2004-doh-art-guidelines.pdf [Accessed: 2014, 12 May]

South Africa. National Department of Health. 2010. Clinical guidelines: PMTCT (Prevention of Mother-to-Child Transmission). Available: http://www.fidssa.co.za/images/PMTCT_ Guidelines.pdf [Accessed: 2014, May 12]

Tukei VJ, Murungi M, Asiimwe AR, et al. Virologic, immunologic and clinical response of infants to antiretroviral therapy in Kampala, Uganda. *BMC Pediatrics* 2013;13:42. [Available at: http://www.biomedcentral.com/1471-2431/13/42]

Violari A, Cotton MF, Gibb, DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008;359:2233-2244.

Violari A, Lindsey JC, Hughes MD et al. Nevirapine versus Ritonavir-Boosted Lopinavir for HIV-Infected Children.*N Engl J Med* 2012;366:2380-9.

World Health Organisation. 2010. Antiretroviral Drugs For Treating Pregnant Women and Preventing HIV Infection in Infants: Recommendations for a Public Health Approach. France: WHO Press. ISBN 978 92 4 159981 8. Available: http://whqlibdoc.who.int/publications/2010/ 9789241599 818_eng. pdf?ua=1 [Accessed: 2014, 12 May]

World Health Organisation. 2013. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach - June 2013. WHO Press. ISBN 978 92 4 150572 7. Available: http://www. who.int/hiv/pub/guidelines /arv2013 /en/ [Accessed: 2014, 12 May]

Zeh C, Weide PJ, Nafisa L, et al. HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of tripleantiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. *PLoS Med* 2011;8(3):e1000430. doi:10.1371/journal.pmed.1000430

Figure 1. Reasons for exclusion from the cohort

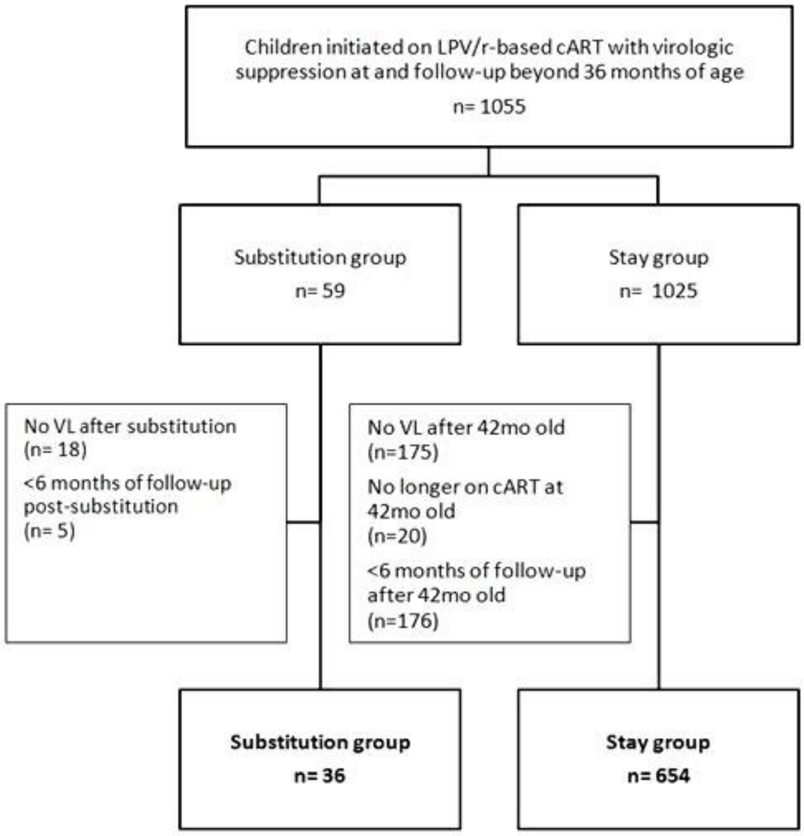

Table 1. Characteristics of children at initiation of cART

		Total	Stay	Substitution	p-value
Sex	Total n (%)	690 (100)	654 (100)	36 (100)	
	Male, n (%)	340 (49.3)	319 (48.8)	21 (58.3)	0.264*
Age (months)	Total n (%)	690 (100)	654 (100)	36 (100)	
	Median (IQR)	17.5 (10.2;23.8)	17.6 (10.3;23.9)	15.3 (8.5; 22.6)	0.381‡
WHO stage 3 or 4	Total n (%)	604 (87.5)	578 (88.4)	26 (72.2)	
	n (%)	540 (89.4)	519 (89.8)	21 (80.8)	0.130†
CD4 %	Total n (%)	556 (80.6)	527 (80.6)	29 (80.6)	
	Median (IQR)	13.9 (9.6; 19.0)	13.9 (9.8; 19.0)	13.0 (7.5; 18.2)	0.571‡
CD4 absolute count (cells/µl)	Total n (%)	554 (80.3)	525 (80.2)	29 (80.6)	
	Median (IQR)	698 (394; 1056)	704 (395; 1057)	626 (364; 946)	0.503‡
Severe immune suppression	Total n (%)	568 (82.3)	539 (82.4)	29 (80.6)	
	n (%)	496 (87.3)	468 (86.8)	28 (96.5)	0.157†
log_{10} HIV-RNA (copies/ml)	Total n (%)	482 (69.8)	462 (70.6)	20 (55.6)	
	Median (IQR)	5.68 (4.97; 6.23)	5.69 (4.99; 6.23)	5.51 (4.80; 6.09)	0.708‡
WAZ	Total n (%)	550 (79.7)	524 (80.1)	26 (72.2)	
	Median (IQR)	-2.34 (-3.51; -1.12)	-2.34 (-3.53; -1.11)	-2.56 (-3.16; -1.27)	0.863‡
PMTCT exposure:	Total n (%)	690 (100)	654 (100)	36 (100)	
None	n (%)	65 (9.4)	59 (9.0)	6 (16.7)	
Unknown	n (%)	503 (72.9)	479 (73.2)	24 (66.7)	0.337*
Initial cART regimen n (%)	Total n (%)	690 (100)	654 (100)	36 (100)	
	D4T, 3TC, LPV/r	558 (80.9)	527 (80.6)	31 (86.1)	
	D4T, 3TC, LPV/r+RTV	94 (13.6)	90 (13.8)	4 (11.1)	
	AZT, 3TC, LPV/r	30 (4.3)	29 (4.4)	1 (2.8)	
	AZT, 3TC, LPV/r+RTV	1 (0.1)	1 (0.1)	0	
	ABC, 3TC, LPV/r	6 (0.8)	6 (0.9)	0	
	ABC, 3TC, LPV/r+RTV	1 (0.1)	1 (0.1)	0	

* Chi-squared, ‡ Wilcoxon rank sum, † Fisher's exact

Table 2. Characteristics of children at 42 months of age (stay group) or at substitution (substitution group)

		Total	**Stay**	**Substitution**	**p-value**
Age (months)	Total n (%)	690 (100)	654 (100)	36 (100)	
	Median (IQR)	42.0 (41.3; 42.6)	41.9 (41.3; 42.6)	44.1 (40.9; 51.8)	0.005 ‡
CD4 %	Total n (%)	635 (92.0)	603 (92.2)	32 (88.9)	
	Median (IQR)	29.3 (24.3; 35.5)	29.6 (24.3; 35.5)	28.5 (25.5; 34.3)	0.562 ‡
CD4 absolute count (cells/µl)	Total n (%)	671 (97.2)	637 (97.4)	34 (94.4)	
	Median (IQR)	1340 (1005; 1768)	1350 (1014; 1780)	1184 (683; 1542)	0.028 ‡
WAZ	Total n (%)	619 (89.7)	589 (90.1)	30 (83.3)	
	Median (IQR)	-0.82 (-1.46; -0.09)	-0.83 (-1.46; -0.09)	-0.58 (-1.36; -0.10)	0.420 ‡
cART regimen	Total n (%)	690 (100)	654 (100)	36 (100)	
	D4T, 3TC, LPV/r	581 (84.2)	581 (88.8)	0	
	D4T, 3TC, LPV/r+RTV	6 (0.9)	6 (0.9)	0	
	AZT, 3TC, LPV/r	28 (4.1)	28 (4.3)	0	
	ABC, 3TC, LPV/r	36 (5.2)	36 (5.5)	0	
	D4T, 3TC, EFV	30 (4.3)	0	30 (83.3)	
	AZT, 3TC, EFV	4 (0.6)	0	4 (11.1)	
	ABC, 3TC, EFV	2 (0.3)	0	2 (5.5)	
	other	3 (0.4)	3 (0.4)	0	
≥ 1 viral blip (VL >400 copies/ml) <36 months old	Total n (%)	690 (100)	654 (100)	36 (100)	
	n (%)	328 (47.5)	318 (48.6)	10 (27.8)	0.015 *

* Chi-squared, † Fisher's exact , ‡ Wilcoxon rank sum
Note: All children had a VL <400 copies/ml because of the eligibility criteria

Table 3. Outcomes

		Total (n=690)	Stay (n=654)	Substitution (n=36)	p-value
Virologic failure#	n (%, with 95% CI)	66 (9.60, 7.47; 12.01)	64 (9.79, 7.62; 12.32)	2 (5.56, 0.68; 18.66)	0.565 ‡
Died	n (%, with 95% CI)	3 (0.43, 0.09; 1.27)	3 (0.46, 0.09; 1.33)	0	1.000 ‡
TFO	n (%, with 95% CI)	287 (41.6, 37.89; 45.37)	278 (42.5, 26.68; 46.40)	9 (25.0, 12.12; 42.20)	0.039 †
LTFU (9mo)	n (%, with 95% CI)	39 (5.7, 4.05; 7.65)	35 (5.4, 3.76; 7.36)	4 (11.1, 3.11; 26.06)	0.139 †
Changed back to LPV/r	n (%, with 95% CI)	-	-	7 (19.4, 8.19; 36.02)	-
Duration on EFV prior to resuming LPV/r (months)	median (IQR)	-	-	5.5 (2.8; 6.6)	-
Observation time from substitution to last visit (months)	median (IQR)	-	-	25.8 (15.1; 34.2)	-
Observation time from cART initiation to last visit (months)	median (IQR)	52.9 (41.6; 64.1)	52.4 (41.4; 63.8)	60.1 (46.6; 67.0)	0.065 ‡
Observation time from 42mo to last visit (months)	median (IQR)	24.5 (18.2; 31.8)	24.4 (18.1; 31.7)	-	-

Defined as 2 consecutive VL measures within 1 year of >1000 copies/ml, ≥1 month apart and after ≥6 months of cART * Chi-squared, † Fisher's exact , ‡ Wilcoxon rank sum

Table 4. Cox regression models: uni- and multivariate hazard ratios

Variable	Unadjusted HR (95%CI)	p-value	Adjusted HR (95% CI)	p-value
VL blip (0=no blips, 1=at least 1 blip)	2.05 (1.43; 2.84)	<0.001	2.23 (1.51; 3.31)	<0.001
WAZ at initiation of cART	0.89 (0.80; 0.99)	0.033	0.87 (0.78; 0.98)	0.021
Duration on cART prior to substitution/42 months old (months)	0.98 (0.96; 1.00)	0.051	0.96 (0.94; 0.99)	0.002
Substitution (0=remained on LPV/r, 1=underwent a LPV/r-to-EFV switch)	1.03 (0.51; 2.11)	0.923	1.43 (0.62; 3.32)	0.401

PART D:

APPENDICES

Appendix 1: IeDEA-SA Manual

IeDEA
International epidemiologic Databases to Evaluate AIDS
Southern Africa

STANDARD PROCEDURE FOR DATA TRANSFER

Version 2.0 / 2010

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

Contents

Lookup tables

1 Introduction

1.1 General remarks

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

1.2 Inclusion criteria for patients

Please include all patients with the following characteristics:

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

Notes:

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

1.3 Dates

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

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

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

patients who commenced HAART at another facility, if the precise date of start of HAART cannot be estimated reasonably accurately, the patient should be entered as treatment experienced and the date of first visit at your facility will be regarded as the date of start of HAART.

1.4 Definitions

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

1.5 Standard codes

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

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

1.6 Data tables

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

- Tables 1 to 5 are required by all sites.
- Table 6 (LINKAGE DATA) is required only for sites that record information on families
- Table 7 (PREGNANCY) is required only for sites that record information on pregnancy electronically.
- Table 8 (PAR HEALTH) is required only for patients who commence care before their 16^{th} birthday.
- Table 9 (TB) is required only from sites that record detailed information on episodes of tuberculosis electronically.
- Table 10 (TRIAL) is required only for sites where patients may be enrolled on clinical trials or research studies apart from cohort analyses of routinely collected data.

- In addition, a table summarising with information on the overall cohort or "meta-data" for the transfer, should be included with all transfers.

1. **PAT (Patient data)**: A table containing socio-demographic data on patients, clinical characteristics at start of HAART in HAART-treated patients, as well as information on the **outcomes** of patients. One line will correspond to one patient. In other words, each patient will appear only once in this table. We propose that this table is called **PAT**.
2. **LAB (Laboratory data at baseline and follow-up)**: This is a single table containing all laboratory data: CD4, HIV viral load, and all other laboratory tests. One line will correspond to one laboratory result. In other words, most patient will have multiple records in this table. We propose that this table is called **LAB**.
3. **ART (Antiretroviral treatments)**: A table with the data on all antiretroviral drugs that a patient has received or been exposed to including PMTCT (both exposure to mother as well as infant peri- or post-natal) or post-exposure prophylaxis. This includes treatment received at your facility and at other facilities. The table will contain one line for each separate drug, with different fields for the drug name (code), the prescription start dates and stop dates. Most patients will have numerous records in this table. The drug history of patients who commence care at your facility but have previously been treated at another facility should be reconstructed and entered into this table as far as possible. We propose that this table be called **ART**.
4. **OI (Opportunistic Events):** A table with the information on all opportunistic infections or incident HIV-associated diagnoses. One line will correspond to one clinical event with different fields for the event type (code), the start dates and stop dates. It is anticipated that stop dates will often not be known. In other words, some patients will have more than one record in this table and some may have no records in this table. History of opportunistic events occurring prior to commencing care at your facility should be reconstructed as far as possible. We propose that this table be called **OI**.
5. **VIS (Visit data)**: A table containing information on all clinical visits (including the first visit at your facility). One line will correspond to one visit. Most patients will have more than one record in this table. We propose that this table be called **VIS**.
6. **LINK (Linkage data)**: A table containing information on family members (partners, children and siblings) also receiving HIV care either within your cohort or at another site. All family members receiving HIV care should be included whether they are receiving care at an IeDEA collaborative site or at a non-IeDEA site. One line will correspond to one family member receiving HIV care. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table is called **LINK**.
7. **PREGNANCY (Pregnancy data):** A table containing information on all pregnancies, including spontaneous abortions/miscarriages and terminated pregnancies, and their outcomes. One line will correspond to one pregnancy. Multiple pregnancies will each have a record in the table, with the outcome of the relevant foetus recorded. Some patients will have more than one record in

this table, while others (including all males and children less than 10 years) will have no records in this table. We propose that this table be called **PREGNANCY**.

8. **PAR_HEALTH (Parental health):** A table with information on parental health status. This table is only required for sites sending data on patients 15 years old and younger at their first visit to the facility. This table is linked to the visit table, so ideally there is an update on parental health status at every

visit. Alternatively, this table should be filled in at least once, either for the first visit at your facility or the date of start of HAART.

9. **TUBERCULOSIS (Tuberculosis data):** A table with information on all episodes of tuberculosis (TB). This table is only for sites that record detailed information on TB episodes. Sites that do not collect detailed information on TB episodes should enter the TB episodes in the OI table. One line will correspond to one TB episode. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table be called **TB**.
10. **TRIAL (Enrolment in trials):** A table with information on any trial or research study (apart from cohort analysis of routinely collected data) on which a patient is enrolled. This table is only for sites running trials or research studies. One line will correspond to one trial/research study on which the patient is enrolled. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table be called **TRIAL**.
11. **MET (Meta-data):** A table comprising key characteristics of the data that is transferred.

2 Variables to be included in core tables

2.1 Socio-demographic characteristics and outcomes (PAT table)

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

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

Table 1 – Variables to be included in PAT table

Name	Format and definitions	Description
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
FACILITY	Text	Text field identifying particular clinic within cohort, if more than facility within the cohort
BIRTH_DMY	DATE (yyyy-mm-dd)	Date of birth Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.

BIRTH_Y	Numeric (for example 1960) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of birth

BIRTH_M	Numeric (for example 8) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of birth
GENDER	Numeric with codes: 1 = Male 2 = Female 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Sex / gender of patient
FRSVIS_DMY	DATE (yyyy-mm-dd)	Date of first visit at facility (Note: This date must be entered exactly)
ENTRY	Numeric with codes (see List 1)	Mode of entry to your facility
ENTRY_OTHER	Text	Details of other mode of entry not listed in List 1
MODE	Numeric with codes (see List 2)	Most probable mode of HIV transmission
HIV_TYPE	Numeric (for example 1) 1 = HIV-1 2 = HIV-2 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Field to distinguish HIV-1 from HIV-2
HIVP_DMY	DATE (yyyy-mm-dd)	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 (yyyy-mm-dd)	Date of HAART initiation (minimum 3 drugs together) Note: This date must be entered exactly. If patient commenced HAART at another facility and the exact date is not known, the patient should be entered as "Treatment experienced" in the EXP_Y field below and the first visit at your facility will be used as the start of HAART date.
FHV_STAGE_WHO	Numeric with codes: 1 = Stage I 2 = Stage II 3 = Stage III 4 = Stage IV 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Clinical WHO stage (I to IV) at time of starting HAART (Enter 88 patients who have not commenced HAART)
FHV_SDI_1	Text (for example PCP - see List 3) 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Stage defining illness-1 at time of starting HAART. (Enter 88 patients who have not commenced HAART) Note: At least FHV_S_SDI_1 should be completed in patients commencing HAART; A maximum of 4 stage defining illness can be entered in the 4 fields provided. There is no specific ordering to the entering of stage defining illnesses.

FHV_SDI_2	Text (for example PCP - see List 3) 0 = No further stage defining illness 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Stage defining illness-2 at time of starting HAART. (Enter 88 patients who have not commenced HAART)
FHV_SDI_3	Text (for example PCP - see List 3) 0 = No further stage defining illness 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Stage defining illness-3 at time of starting HAART. (Enter 88 patients who have not commenced HAART)
FHV_SDI_4	Text (for example PCP - see List 3)	Stage defining illness-4 at time of starting HAART. (Enter 88 patients who have not

	0 = No further stage defining illness 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	commenced HAART)
EXP_Y	Numeric with codes: 0 = No (No previous ARV experience) 1 = Yes (Treatment experienced, drug history known and recorded in ART table) 2 = Yes (Treatment experienced, drug history not known) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient is treatment experienced prior to starting HAART (HAART_DMY) ? Experienced = Any ARV drug (single or dual therapy) for at least 30 days before starting HAART (PMTCT regimen and PEP excluded). This field can also be used in patient has interrupted ART and prior ART start date unknown. This should be entered for all patients even those who have not commenced HAART.
MTCT_Y	Numeric with codes: 0 = No (No MTCT exposure) 1 = Yes (MTCT exposed, drug history reconstructed and recorded in ART table) 2 = Yes (MTCT exposed, drug history not reconstructable) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient exposed to MTCT drugs (either mother during pregnancy or infant peri- or post-natally) prior to start of HAART (HAART_DMY)? This should be entered for all patients even those who have not commenced HAART.
PEP_Y	Numeric with codes: 0 = No (No PEP exposure) 1 = Yes (PEP exposed, drug history reconstructed and recorded in ART table) 2 =Yes (PEP exposed, drug history not reconstructable) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient exposed to post-exposure prophylaxis (PEP) drugs prior to start of HAART (HAART_DMY)? This should be entered for all patients even those who have not commenced HAART.
TB_FHV	Numeric with codes 0 = No 1 = Yes 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Patient was on treatment for TB at start of HAART (HAART_DMY) (Enter 88 patients who have not commenced HAART)

WKS_TB_FHV	Numeric (for example 8) 88=Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Duration in weeks since start of TB treatment when HAART was commenced in patients with TB at start of HAART (Enter 88 for patients who have not commenced HAART or who did not have TB at start of HAART)

PREG_FHV	Numeric with codes 0 = No 1 = Yes 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Pregnant at start of HAART (Enter 88 for men and children <10 years old AND all patients who have not commenced HAART)
METHOD_INTO_ART	Numeric with below codes 0 = New 1 = Transfer in 88= Not applicable	Method into ART at current clinic: If patient is new to ART or considered treatment experienced and re-starting ART at your clinic (please see EXP_Y) then they are 'New'. If patient is coming to you clinic on ART then patient is considered a 'transfer in'. (Enter 88 for all patients not yet on ART)
TRANSFER_IN_DATE	DATE (yyyy-mm-dd)	Date of first visit in your clinic (Leave blank if patient is not considered a transfer in)
FROM_LOCATION	Numeric with below codes 0 = Within province 1 = From other province 2= From other country 88= Not applicable	This is the location the patient transferred from while on ART. (Enter 88 for all patients not yet on ART and for all patients who are not considered a 'transfer in')
LAST_CONTACT_DMY	DATE (yyyy-mm-dd)	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 (yyyy-mm-dd)	Date of outcome (Leave blank if outcome is Alive [in care] or Alive [not in care])
OUTCOME_Y	Numeric (e.g. 2004) 8888 = Not applicable or exact date of outcome entered above 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of outcome Enter 8888 for patients who have not died, or if exact date of outcome entered above.

OUTCOME_M	Numeric (e.g.12) 88 = Not applicable or exact date of outcome entered above 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of outcome Enter 88 for patients who have not died, or if exact date of outcome entered above.
DEATH_C1	Numeric with codes (see List 6)	Cause of death : Enter 88 for patients who have not died

		Note : There are 3 fields for 3 causes of death to be entered in no specific order. If an HIV-related cause of death is recorded, please ensure that the condition is recorded appropriately in the OI table. Nature of contribution of cause: For each cause of death, please characterise the contribution of the specific cause.
DEATH_N1	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	
DEATH_C2	Numeric with codes (see List 6)	
DEATH_N2	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	
DEATH_C3	Numeric with codes (see List 6)	
DEATH_N3	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	
CAREG	Numeric with codes (see List 7)	Primary caregiver at start of HAART (HAART_DMY) (paediatric patients only – enter 88 for adult patients)
DISCL_CG	Numeric with codes (see List 8)	Person informed of the HIV status of the child (paediatric patients only – enter 88 for adult patients)

DISCL_CHILD	Numeric with codes 0 = No 1 = Yes 2 = In process 88 = Not applicable (adult patient) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Was the child informed of his/her status at HAART_DMY? (paediatric patients only - enter 88 for adult patients)
DELIV_M	Numeric with codes 10 = Vaginal, spontaneous 11 = Vaginal, forceps 12 = Vaginal, vacuum 20 = Caesarean section – primary/elective (before onset of labour and rupture of membranes)	Mode of delivery (paediatric patients only - enter 88 for adult patients)
	21 = Caesarean section – 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)
BRSTFD	Numeric with codes 10 = breastfeeding, exclusive 11 = breast-feeding, exclusivity unknown 12 = mixed feeding 20 = Formula feeding 88 = Not applicable 95 = Not ascertained 99 = Unknown, despite attempting ascertainment	Main infant feeding option after birth (paediatric patients only - enter 88 for adult patients)
BRSTFD_ED	DATE (dd-mm-yy)	Date of cessation of breast feeding if applicable Leave blank if not applicable, child still being breastfed, date not known, or child not breastfed at all.

BRSTFD_EST_DUR	Numeric (e.g. 2) 77 = still breast-feeding, ED unknown 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Estimated duration of breastfeeding in months in children who are exclusively breastfed or mixed fed. (paediatric patients only - enter 88 for adult patients) Enter 88 if child still being breastfed or child not breastfed at all.

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

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

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

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

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

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

Codes	Description	WHO stage (Adult)	WHO stage (Paed)	Event (Adult)	Event (Paed)	SDI (Adult)	SDI (Paed)
ANGC*	Angular cheilitis	2	2	1	1	1	1
BCGD	BCG disease – disseminated	4	4	1	1	1	1
BCGL*	BCG Lymphadenitis (localised to R axilla)	88	88	1	1	0	0
BCGP*	BCG Pulmonary	88	88	1	1	0	0
BCIR*	Recurrent severe presumed bacterial infection (excluding pneumonia)	4	4	0	0	1	1
BCIS*	Severe presumed bacterial infection – single episode (excluding pneumonia)	88	88	1	1	0	0
BCNE	Bacterial pneumonia, recurrent (>2 episodes within 1 year)	4	3	0	0	1	1
BCNS*	Severe presumed bacterial pneumonia (single episode)	88	88	1	1	0	0
BLD*	Unexplained anaemia (<8g/dl), and or neutropaenia (<500/mm3 – 2; <1000/mm3 - children), and or thrombocytopaenia (<50000/mm3) > 1 month	3	3	0	0	1	1
CANM*	Candidiasis (oral) (outside neonatal period)	3	3	1	1	1	1
CANO	Candidiasis oesophogeal	4	4	1	1	1	1
CANT*	Candidiasis (trachea, bronchi or lungs)	4	4	1	1	1	1
CLD*	Chronic HIV-associated lung disease	88	3	0	1	0	1
CMO*	HIV-associated cardiomyopathy	88	4	1	1	0	1
CMVO	Cytomegalovirus other location (site other than liver, spleen or lymph nodes) (onset at age>1month)	4	4	1	1	1	1
CMVR	Cytomegalovirus (CMV) chorioretinitis (onset at age>1month)	4	4	1	1	1	1
CRCO	Cryptococcosis extrapulmonary	4	4	1	1	1	1
CRSP	Cryptosporidiosis (duration > 1 month)	4	4	0	0	1	1
CRSPS*	Cryptosporidiosis ?	88	88	1	1	0	0
CRVC	Cervical cancer (invasive)	4	88	1	1	1	0
DEM	AIDS dementia complex	4	88	1	0	1	0
DIAC*	Unexplained chronic diarrhoea (> 1month for adults; >14 days for children)	3	3	0	0	1	1
DIAS	Diarrhoea (duration <1 month - adults; <14 days - children)	88	88	1	1	0	0
ENC*	HIV encephalopathy	4	4	1	1	1	1
FBLS	Focal brain lesion	88	88	1	1	0	0
FEVC*	Unexplained persistent fever (> 1 month)	3	3	0	0	1	1
FNID*	Fungal nail infections (fingers or toes)	88	2	0	1	0	1
FNIF*	Fungal nail infections of fingers	2	88	1	0	1	0
HERP	Herpes simplex virus ulcers (duration > 1 month)	4	4	0	0	1	1

HERPS*	Herpes simplex virus ulcers	88	88	1	1	0	0
HERPV*	Visceral herpes simplex infection	4	4	1	1	1	1
HG	Hodgkins Lymphoma	88	88	1	1	0	0
HIST	Histoplasmosis extrapulm.	4	4	1	1	1	1
HPVE*	Extensive human papilloma virus infection	88	2	1	1	0	1
HSM*	Hepatosplenomegaly	88	2	0	0	0	1
HZM*	Herpes zoster (more than one dermatome)	88	88	1	1	0	0
HZS*	Herpes zoster (single dermatome)	2	2	1	1	1	1
ISDI	Isosporiasis diarrhoea (duration > 1 month)	4	4	0	0	1	1
ISDS*	Isosporiasis diarrhoea	88	88	1	1	0	0
KS	Kaposi Sarcoma	4	4	1	1	1	1
LEIS	Leishmaniasis visceral	4	88	1	1	1	0
LEU	Progressive multifocal leucoencephalopathy	4	4	1	1	1	1
LGE*	Lineal gingival erythema	88	2	1	1	0	1
LIP*	Lymphoid interstitial pneumonitis	88	3	0	1	0	1
MC	Mycobacterium avium complex (MAC) or Kanasii extrapulm.	4	4	1	1	1	1
MCDI	Microsporidosis diarrhoea (duration > 1 month)	4	4	0	0	1	1
MCDS*	Microsporidosis diarrhoea	88	88	1	1	0	0
MCI*	Mycobacterium Immune reconstitution syndrome	88	88	1	1	0	0
MCP	Mycobacterium tuberculosis pulmonary	3	3	1	1	1	1
MCPO	Mycobacterium pulmonary other (excluding BCG in children)	88	88	1	1	0	0
MCX	Mycobacterium tuberculosis extrapulmonary	4	4	1	1	1	1
MCXO	Mycobacterium extrapulm. other (excluding BCG in children)	4	4	1	1	1	1
MNUM*	Moderate unexplained malnutrition (6080% EWFA)	88	3	0	1	0	1
MNUS*	Unexplained severe wasting or malnutrition (<60% EWFA)	88	4	0	1	0	1

MOLC*	Extensive molluscum contagiosum	88	2	1	1	0	1
MYCD*	Any disseminated mycosis	4	4	1	1	1	1
NHG	Non-Hodgkin Lymphoma, not specified	88	88	1	1	0	0
NHGB	Non-Hodgkin Lymphoma, Burkitt (classical or atypical)	88	88	1	1	0	0
NHGI	Non-Hodgkin Lymphoma, diffuse large B-cell lymphoma (immunoblasti or centroblastic)	4	4	1	1	1	1
NHGP	Non-Hodgkin Lymphoma primary brain lymphoma	4	4	1	1	1	1
NHGU	Non-Hodgkin Lymphoma unknown/other histology	88	88	1	1	0	0
NPO*	HIV-associated nephropathy	88	4	1	1	0	1
NUS*	Acute necrotising ulcerative stomatitis, gingivitis or periodontitis	3	3	1	1	1	1
OHLP*	Oral hairy leukoplakia	3	3	1	1	1	1
ORUL*	Recurrent oral ulcerations	2	2	0	0	1	1
PARE*	Parotid enlargement	88	2	1	1	0	1

PCP	Pneumocystis carinii pneumonia	4	4	1	1	1	1
PGL*	Persistent Generalized Lymphadenopathy	1	1	0	0	1	1
PPE*	Papular pruritic eruptions	2	2	1	1	1	1
RTIL*	Lower respiratory tract infection (other than presumed pneumonia) ?	88	88	1	1	0	0
RTIR*	Recurrent or chronic respiratory tract infection (RTIs, sinusitis, bronchitis, otitis media, otorrhea, pharyngitis)	2	2	0	0	1	1
RTIU*	Upper respiratory tract infection	88	88	1	1	0	0
RVF*	Acquired HIV-associated recto-vaginal fistula	88	4	1	1	0	1
SAME	Salmonella bacteraemia (non-typhoid) (single episode)	88	88	1	1	0	0
SAM	Salmonella bacteraemia (non-typhoid) recurrent	4	88	0	0	1	0
SEBD*	Seborrheic dermatitis	2	2	1	1	1	1
TOX	Toxoplasmosis brain (outside neonatal period)	4	4	1	1	1	1
WAST	HIV Wasting Syndrome	4	88	1	0	1	0
WTLM*	Moderate unexplained weight loss (<10% of body weight)	2	88	1	0	1	0
WTLS*	Severe unexplained weight loss (>10% of body weight)	3	88	1	0	1	0

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

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

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

Codes	Mode of infection
10	Death (HIV-related)
11	Death (HIV relationship unknown)
12	Death (not HIV-related)
20	Alive and in care at your facility
21	Known to be alive and in care at another facility
22	Known to be alive and patient is not in care
23	Known to be alive but not known whether patient is in care

30	Transfer out within the same service, vital status after transfer out unknown
31	Transfer out to a different service, vital status after transfer out unknown
40	Loss to follow-up despite active tracing attempted
41	Loss to follow-up (not actively traced)
90	Other
95	Not ascertained

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

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

Codes	Cause of Death
1	Myocardial Infarction
2	Stroke
3	Other cardiovascular diseases
4	Symptoms caused by mitochondrial toxicity
4.1	Lactic acidosis
5	Complications due to diabetes mellitus
6	Pancreatitis
7	Complications due to hepatitis
7.1	Hepatitis related
7.2	Liver failure not related to hepatitis or mitochondrial toxicity
8	HIV-related
8.1	AIDS defining event
8.2	Invasive bacterial infection
9	Renal failure
10	Bleeding (haemophilia)
20	Non AIDS defining cancer
88*	Not applicable
90	Other
91	Suicide
92	Drug Overdose
93	Accident
95*	Not ascertained
99	Unknown, Fatal case with no information

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

Codes	Primary caregiver
1	Mother
2	Father

3	Grandmother
4	Other family member
5	Institution
6	None
90	Other
88	Not applicable
95	Not ascertained
99	Unknown despite attempting ascertainment

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

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

2.2 Laboratory data (LAB table)

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

Notes:

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

- There is no code for unknown values of for laboratory test results as tests of which the result is unknown should not be included in the dataset.
- Only dates in the DMY format are permissible in this table

Table 2 – Variables to be included in the table LAB

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
LAB_DMY	Date (yyyy-mm-dd)	Date when specimen was taken
LAB_ID	Text (see List 9)	Code representing the measurement
LAB_V	Numeric (for example 44)	Numeric value of measurement Leave blank if result entered as code (LAB_C)
LAB_T	Text Lower than limit of detection for viral loads should be entered as “LDL” TB microscopy and culture results should be entered as follows: - Paucibacillary 1+ 2+ 3+ Unknown +	Text result eg. “> 6 000 000” or “P+++” Leave blank if result entered as number (LAB_V)
RNA_L	Numeric -88 = Not applicable -99 = Unknown	Lower limit of detection of RNA assay (Enter -88 for laboratory tests other than viral load)
TB_DRUG	Text with codes: INH_L = Isoniazid low dose	TB Drug against which sensitivity has been tested. (Enter 88 for laboratory tests other than viral
	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	load)
DRUG_RES	Numeric with codes: 0 = No (Sensitive) 1 = Yes (Resistant) 88 = Not applicable	Is Mycobacterium TB cultured **RESISTANT** to drug in TB-DRUG field? (Enter 88 for laboratory tests other than viral load)

List 9: Codes for measurement type (LAB_ID)

*Code source: HICDEP codes; new codes denoted by **

Table name: LU :LAB :LAB_ID

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

2.3 Antiretroviral drug variables (ART table)

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

Notes:

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

Table 3 – Variables to be included in ART table

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
ART_ID	ATC (for example NVP – see List 10)	Type of antiretroviral drug
ART_SD_DMY	Date(yyyy-mm-dd)	Date of starting each antiretroviral drug (start date). Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.

ART_SD_Y	Numeric (e.g. 2003) 8888 = Exact start date entered in appropriate field 9999 = Unknown despite attempting ascertainment 9995 = Not ascertained	Year of starting drug
ART_SD_M	Numeric (e.g. 7) 88 = Exact start date entered in appropriate field 99 = Unknown despite attempting ascertainment 95 = Not ascertained	Month of starting drug
ART_RS	Numeric with codes (See List 11)	Reason for receiving ART
ART_FORM	Numeric with codes 1 = Tablet/capsule 2 = Syrup/Suspension 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Type of formulation

ART_COMB	Numeric with codes 1 = Individual drug 2 = Part of a fixed dose combination 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Is drug part of a fixed dose combination?
ART_ED_DMY	Date(yyyy-mm-dd)	Date of stopping each antiretroviral drug (end date) Enter exact date in this field if known. If unknown leave blank and enter **EITHER** month and year as far as possible in fields below **OR** number of doses **OR** duration in weeks in the appropriate fields.
ART_ED_Y	Numeric (e.g. 2004) 8888 = exact end date or number of doses or duration in weeks entered in appropriate fields 9999 = Unknown despite attempting ascertainment 9995 = Not ascertained	Year of stopping drug

ART_ED_M	Numeric (e.g. 7) 88 = exact end date or number of doses or duration in weeks entered in appropriate fields 99 = Unknown despite attempting ascertainment 95 = Not ascertained	Month of stopping drug
NO_DOSES	Numeric (e.g. 1) 888 = end date or duration in weeks entered in appropriate fields 999 = Unknown despite attempting ascertainment 995 = Not ascertained	Number of doses of drug e.g. 1 for single dose Nevirapine
NO_WEEKS	Numeric (e.g. 12) 888 = end date or number of doses entered in appropriate fields 999 = Unknown despite attempting ascertainment 995 = Not ascertained	Number of weeks of receiving drug e.g. 12 for AZT from 28 weeks of pregnancy delivering at term
ART_END_RS	Numeric with codes (See List 12)	Reason for stopping antiretroviral drug
INFO_SOURCE	Numeric with codes 1 = Clinical records at this facility 2 = Clinical records/letter from	Source of information about ART
	another facility 3 = Patient/caregiver report 4 = Likely protocol in use 90 = Other 99 = Unknown	

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

ATC codes	Antiretroviral treatment
J05A	Drug unspecified (i.e. single drug, totally unknown)
J05AE	PI unspecified
J05AE01	Saquinavir (gel, not specified)
J05AE01-SQH	Saquinavir hard gel (INVIRASE)
J05AE01-SQS	Saquinavir soft gel (FORTOVASE)
J05AE02	Indinavir (CRIXIVAN)
J05AE03	Ritonavir (NORVIR)
J05AE03-H	Ritonavir high dose (NORVIR)
J05AE03-L	Ritonavir low dose (NORVIR)

J05AE04	Nelfinavir(VIRACEPT)
J05AE05	Amprenavir (141W94) (AGENERASE)
J05AE06	Lopinavir/Ritonavir (ABT-378/r, Kaletra)
J05AE07	Fosamprenavir
J05AE-ATV	Atazanavir (ZRIVADA)
J05AE-GW4	GW433908/VX-275 (Drug phase III) (PROGENERASE)
J05AE-TMC	TMC 114 (Tibotec)
J05AE-TPR	Tipranavir (trial drug)
J05AF	NRTI unspecified
J05AF01	Zidovudine (AZT, RETROVIR)
J05AF02	Didanosine (ddI) (VIDEX)
J05AF03	Zalcitabine (ddC) (HIVID)
J05AF04	Stavudine (d4T) (ZERIT)
J05AF05	Lamivudine (3TC, EPIVIR)
J05AF06	Abacavir (1592U89) (ZIAGEN)
J05AF07	Tenofovir (TDF, VIREAD)
J05AF08	Adefovir (PREVEON)
J05AF09	Emtricitabine (FTC, EMTRIVA)
J05AF10	Entecavir
J05AF30-KIV	Kivexa
J05AF30-TZV	Trizivir
J05AF-FOZ	Fozivudinetidoxi
J05AF-LDN	Lodenosine (trialdrug)
J05AG	NNRTIunspecified
J05AG01	Nevirapine (VIRAMUNE)
J05AG01-SD	Nevirapine (VIRAMUNE) single dose
J05AG02	Delavirdine (U-90152) (RESCRIPTOR)
J05AG03	Efavirenz (DMP-266) (STOCRIN, SUSTIVA)
J05AG-LOV	Loviride
J05AG-TMC	TMC 125 (Tibotec)
J05A-PBT	Participant in Blinded Trial
J05AR*	ART regimen and drug unspecified (i.e. both number and names of drugs totally unknown)
J05AX07	Enfurvirtide (FUZEON, T-20/Ro 29-9800)
L01XX05	Hydroxyurea/Hydroxycarbamid (LITALIR)

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

Codes	Reason
10	MTCT – antenatal (mother)
11	MTCT – peripartum (mother)
12	MTCT – postpartum (mother)
13	MTCT – timing unknown (mother)
20	MTCT – peripartum (infant)

21	MTCT – postpartum (infant)
22	MTCT – timing unknown (infant)
30	ARV as treatment
40	PEP
95	Not ascertained
99	Unknown despite attempting ascertainment

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

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

94.1	Non-compliance				1
95	Physician's decision, not specified above (note overlap with standard code				1
95.1*	Contra-indication expired				1
96	Pregnancy		1		
96.1*	MTCT regimen completed				1
96.2*	Pregnancy ended				1
97	Study treatment				1
98	Other causes, not specified above				1
99	Unknown despite attempting ascertainment				1
99.5	Not ascertained				1

2.4 Opportunistic events (OI table)

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

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

Table 4 – Variables to be included in OI table

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
OI_ID	Text (for example PCP - see List 3 – Disease codes – under PAT table)	Type of opportunistic event
OI_SD_DMY	Date(yyyy-mm-dd)	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	Month of start of event
	(Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	
OI_ED_DMY	Date(yyyy-mm-dd)	Date of end of each opportunistic event. Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below If OI is ongoing (has not yet ended) leave blank and enter appropriate code in field below

OI_ED_Y	Numeric (e.g. 2001) 8885 = Ongoing 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of end of event
OI_ED_M	Numeric (e.g. 11) 85 = Ongoing 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of end of event
DIAG_METH	Numeric (see List 13)	Method of diagnosis

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

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

2.5 Follow-up clinic visits (VIS table)

Table 5 below details the clinical visit information. 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 (yyyy-mm-dd)	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)
TB_STATUS	Numeric with codes 0 – No symptoms 2– Symptoms with sputum 3 – Symptoms no sputum 4 – On TB treatment 95– Not screened 99– Screening status unknown	Patient's TB status on date of clinical visit.
WHO_STAGE	Numeric with codes: 1 = Stage I 2 = Stage II 3 = Stage III 4 = Stage IV 95 = Not ascertained	Clinical WHO stage (I to IV) on date of visit
CTX	Numeric with codes : 1 = yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Cotrimoxazole status
INH	Numeric with codes : 1 = Yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Isoniazid status
FLU	Numeric with codes : 1 = Yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Fluconazole status
HEADC	Numeric (for example 75)	Head circumference in centimeters (cm)
SCHOOL_Y	Numeric with codes	Schooling for children >5 years.
	0 = No school 1 = At school 88 = Not applicable 95 = Not ascertained	For adults and children less than 5 years, enter 88.

2.6 Demographic Information (DEM table)

Table 6 below details the data that should be included in DEM table.

Table 6 – Variables to be included in DEM table

Name	Format and definitions	Description
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
FOLDER_NUMBER	Text	Text field identifying the unique patient folder number.

OTHER_NUMBER	Text	Text field identifying any other unique patient identifier e.g. Passport number.
SURNAME	Text	Patient's last name.
FIRST_NAME	Text	Patient's first name.
BIRTH_DATE	Date (yyyy-mm-dd)	Date of birth Enter exact date in this field if known.
DEATH_DATE	Date (yyyy-mm-dd)	Date of death Enter exact date in this field if known.
GENDER	Text. The following options exist: 1 = Male 2 = Female 95 = Indeterminate	Sex / gender of patient
RACE	Text. The following options exist: - Asian - Black - Coloured - White - Other	Race of patient.
HOME_ADDRESS_1	Text	Address details for the patient
HOME_ADDRESS_2	Text	Address details for the patient
HOME_ADDRESS_3	Text	Address details for the patient
HOME_ADDRESS_4	Text	Address details for the patient
POST_CODE	Text	Postal code for area or suburb that the patient resides.
CELL_NUMBER	Text	Cell phone number of patient.
MARITAL_STATUS	Text (e.g. Divorced, Married)	Marital status of patient.
HOME_LANGUAGE	Text (e.g. English, Afrikaans, Isixhosa)	Language used by patient at home.

3 Variables to be included in additional tables

3.1 Family and partner linkages (LINK table)

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

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

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

Table 6 – Variables to be included in the table LINK

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

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

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

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

Codes	Cohort
Cohort ID	Cohort description

3.2 Pregnancy information (PREGNANCY table)

Table 7 details information to be included in the PREGNANCY table. This table contains information on all pregnancies since the patient was known to be HIVinfected, 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 (yyyy-mm-dd)	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 (yyyy-mm-dd)	Exact date of delivery, spontaneous abortion or termination Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
PREG_END_Y	Numeric (e.g. 2003) 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of delivery, spontaneous abortion or termination
PREG_END_M	Numeric (e.g. 9) 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of delivery, spontaneous abortion or termination
PREG_ED	Numeric (e.g. 36) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Estimated duration of entire pregnancy in weeks
PREG_OUTCOME	Numeric with codes 1 = Live birth 2 = Still birth 3 = Termination of pregnancy 4= Spontaneous abortion (miscarriage) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Outcome of pregnancy
INF_WT	Numeric (e.g. 2.9) 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Weight of delivered infant. If spontaneous abortion or termination, enter 88

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

3.3 Parental Health (PAR_HEALTH table)

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

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

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

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

Table 8: Variables to be included in the PAR_HEALTH table

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

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

3.4 Tuberculosis information (TB table)

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

Table 9 – Variables to be included in the table TB

Name	Format	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
REG_DMY	Date (dd/mm/yy)	Date registered with TB
REGID	Text (eg. 2272007) -95 = Not ascertained -99 = Unknown despite attempting ascertainment	TB register number

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

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

3.5 Trial/research study enrolment information (TRIAL table)

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

Table 11 – Variables to be included in the table TRIAL

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

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

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

4 Meta-data

This table contains information about the data transfer itself.

Table 12 – Variables to be included in the table META

Name	Format	Description
COHORT	Text	Name of the cohort
ENROLS_DMY	Date (yyyy-mm-dd)	Date of start of enrolment
ENROLE_DMY	Date (yyyy-mm-dd)	Date of end of enrolment
FU_CLOSE_DMY	Date (yyyy-mm-dd)	Date of last possible follow-up
ASC_DMY	Date (yyyy-mm-dd)	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 (yyyy-mm-dd)	Date extracted
EMAIL	Text	Email address of site person responsible

Appendix 2: 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.

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 postprint (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, andadolescents.

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 Email 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

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

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

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 postprint (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

Appendix 3: UCT Human Research Ethics Committee Approval for this study

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] 404 7682 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

29 July 2014

HREC REF: 526/2014

Dr M Davies
Public Health & Family Medicine
Falmouth Building

Dear Dr Davies

PROJECT TITLE: VIROLOGIC OUTCOMES OF HIV-INFECTED CHILDREN UNDERGOING A SINGLE-CLASS DRUG SUBSTITUTION FROM LOPINAR/RITONAVIR-TO EFAVIRENZ-BASED ANTIRETROVIRAL TREATMENT: A RETROSPECTIVE COHORT STUDY- LINKED TO 084/2006 (Masters candidate KL Reichmuth)

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 July 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/fhs/research/humanethics/forms)

We also acknowledge that Masters student Dr Kirsten Reichmuth is also 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

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Appendix 4: UCT Human Research Ethics Committee Approval for IeDEA-SA

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HEALTH SCIENCES FACULTY ETHICS COMMITTEE
23 MAY 2014
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 2015
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	25/5/2014

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	21 May 2014		
HREC REF Number	084/2006	Current Ethics Approval was granted until	15 May 2014
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	20 May 2014
Signature of Supervisor (if PI is a student)		Date	

26 July 2012 Page 1 of 1 FHS017
(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)

Appendix 5: Supplementary material (Manuscript Table 4.)

Table 4. Children in whom LPV/r-based cART was re-instituted

	Child 1	Child 2	Child 3	Child 4	Child 5	Child 6	Child 7
Exposed to PMTCT antiretrovirals	yes	yes	unknown	yes	unknown	unknown	unknown
Age cART started (months)	6.4	22.6	29.6	25.2	24.0	22.6	18.7
Blips prior to 36mo of age	unknown	yes	yes	yes	no	no	yes
Age at LPV/r to EFV (months)	40.6	39.1	39.9	51.1	40.9	56.3	37.0
Duration on EFV (months)	5.5	10.2	1.9	2.8	5.5	2.8	6.6
Reason for re-initiating LPV/r	VL 12 000 copies/ml after 2 months on EFV	met criteria for virologic failure* on EFV	unknown	unknown	unknown	unknown	met criteria for virologic failure* on EFV
Outcome	Re- supressed on LPV/r TFO	No further VL on LPV/r retained in care	cART stopped: non-adherent TFO	Remained supressed on LPV/r TFO	Remained supressed on LPV/r TFO	Remained supressed on LPV/r TFO	Re-supressed on LPV/r retained in care
Cohort	HS	HS	HS	HS	HS	HS	RM

*After substitution, failure defined as 2 consecutive HIV-RNA measures within 1 year of >1000copies/ml, ≥1 month apart OR if listed as the reason for drug substitution