A description of HIV-exposed uninfected infants in the IeDEA Southern Africa Cohort and an examination of growth outcomes

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Declaration

I, Erna Morden (MRDERN001), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and has not, in whole or in part, been submitted towards another degree, at this university or elsewhere.

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Dissertation précis

Since the successful use of antiretroviral therapy for the prevention of mother-to-child transmission of human immunodeficiency virus (HIV), there has been a steady increase in the number of infants born to HIV-infected mothers who remain uninfected. The characteristics of these HIV-exposed uninfected infants are not well known, including growth and other health outcomes.

The International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) research strategy 2011-2016 includes specific studies in pregnant women, infants, children and adolescents. This study addresses one of the IeDEA-SA objectives, namely to establish and describe a sub-cohort of HIV-infected pregnant women and their exposed infants. Part A, the protocol, includes background information on sites contributing to this cohort of HIV-exposed uninfected (HEU) infants. It also details the aims, objectives and methodology of this study.

Part B, the literature review, discusses what is known about HIV-exposed uninfected infants to date. It includes maternal disease factors, the use of antiretroviral therapy and the association between feeding modality and growth, focussing on studies conducted on the African continent.

Part C, the manuscript, details the methodology, results and their interpretation of longitudinal analysis of growth among HEU infants in the IeDEA-SA collaboration. This cohort of HEU infants included 2621 infants from two South African sites. The median birth WAZ was -0.65 (IQR -1.46; 0.0), 51% were male and there was a median of 2 visits per infant. The feeding modalities practised were as follows: 0.5% exclusive breastfeeding, 7.9% unknown breastfeeding exclusivity, 78.6% mixed breastfeeding and 10.6% formula feeding. Mothers with a CD4 <200 cells/µl delivered infants with a lower birth WAZ (adjusted ß -0.253 [95% CI -0.043; -0.072], p = 0.006) compared to mothers with a CD4 ≥500 cells/µl. Similarly,

mothers who did not receive antiretroviral (ARVs) drugs delivered infants with a lower birth WAZ (adjusted ß -0.49 [95% CI -0.78; -0.20], p = 0.001) compared to mothers who received antenatal ARVs. Antenatal maternal ARVs and CD4 cell count did not have an effect on postnatal growth. Mixed effects models using maximum likelihood estimation for the longitudinal analysis of growth showed that exposure to breast milk positively influenced growth, albeit the effect was small. Infants with a birth weight <2 500g (ß 0.069 [95% CI 0.061; 0.078], p <0.0001) experienced faster growth within the first 28 weeks of life compared to infants with a birth weight ≥2 500g. In this cohort of South African HEU infants, less severe maternal disease and the use of ARVs positively impacted birth weight. Mixed feeding was common, and any breastfeeding may have a positive effect on longitudinal growth.

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Phil 4:13

Acronyms and abbreviations

ART	Antiretroviral therapy
ARVs	Antiretroviral drugs
BF	Breastfeeding/breastfed
EBF	Exclusive breastfeeding
EFF	Exclusive formula feeding
FF	Formula feeding
FTC	Emtricitabine
HAART	Highly active antiretroviral therapy
HEU	HIV-exposed uninfected
HIV	Human Immunodeficiency Virus
IeDEA-SA	International Epidemiologic Databases to Evaluate AIDS, Southern Africa
IQR	Inter-quartile range
MBF	Mixed breastfeeding
MF	Mixed feeding
MFF	Mixed formula feeding
NBF	Not/never breastfed
NVP	Nevirapine
PaBF	Partial breastfeeding
PMTCT	Prevention of mother-to-child transmission
PrBF	Predominant breastfeeding
sdNVP	Single dose nevirapine
TDF	Tenofovir
WHO	World Health Organization
ZDV	Zidovudine
ZEBS	Zambia Exclusive Breastfeeding study
ZVITAMBO	Zimbabwe Vitamin A for Mothers and Babies Project

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Part A: Protocol

I. Summary

HIV-exposed uninfected (HEU) infants are a growing population in southern Africa. The 2010 South African antenatal survey reports a 30.2% prevalence of HIV infection among pregnant women. Most of the infants born will be exposed but not infected. These infants are an overlooked group vulnerable to morbidity and mortality. We aim to describe the characteristics of HEU infants within the IeDEA-SA network and examine feeding practices and growth outcomes.

II. Introduction

1. Background

HIV-exposed uninfected children (HEU) are a growing population in southern Africa. Nearly 40% of infants are born to HIV-infected mothers and the majority of these are likely to be uninfected [1]. Specifically, in South Africa in 2010, the prevalence of HIV infection among pregnant women was 30.2% [2]. These exposed uninfected children are an overlooked group of children at high risk of both morbidity and mortality [3].

Much research has been conducted examining HIV-infected women in Africa but most of this research has been focused on the prevention of mother-to-child transmission (PMTCT) via antiretroviral therapy (ART) and infant feeding modality [4].

Long-term consequences of *in utero* ARVs

Knowledge of the long-term impact of *in utero* exposure to antiretrovirals (ARVs) on growth and development is limited and most studies that have examined outcomes of *in utero* ARV exposure have had relatively brief follow-up periods [5]. HIV-exposed African infants are not only exposed to *in utero* ARVs but also through breastfeeding as ARVs are present in breast milk if mothers are on antiretroviral therapy [4]. Such exposure is likely to become more frequent as countries increasingly move to adopt option B/B+ in terms of the World Health Organization (WHO) guidelines [6]. The distinction between developed and developing countries is evident as in developed countries most HIV-exposed infants are formula fed. In contrast, in developing countries, formula feeding is only recommended by the WHO if it is affordable, feasible, acceptable, safe and sustainable (AFASS criteria) [4, 7]. South Africa recently changed its HIV-exposed infant feeding policy to support breastfeeding with the use of ARVs to prevent transmission rather than formula feeding by HIV infected mothers [8]. The policy states that if mothers are on lifelong ART, infants are to receive nevirapine (NVP) for 6 weeks but if mothers are not on lifelong ART, infants are to receive NVP for prophylaxis until the cessation of breastfeeding [8].

Infant feeding and HIV

The safest feeding option for all infants, for those who are unexposed to and those who are exposed to HIV (particularly in resource-limited settings), is exclusive breastfeeding [9] but there have been conflicting infant feeding messages for HIV infected mothers [4, 10]. A study in Malawi [11] examined the effects of the cessation of breastfeeding among HEU infants and found that not breastfeeding was significantly associated with higher mortality after adjustment for possible confounders including extended ART prophylaxis. There is a

dilemma between protecting exposed uninfected infants from the negative consequences of not breastfeeding and keeping these infants HIV free as the virus is known to be transmitted via breast milk [11].

Infant growth and ARVs

The effect of ARV exposure on postnatal growth has been examined in numerous studies. Two cohorts in Botswana showed that HEU infants exposed to highly active antiretroviral therapy (HAART) had lower anthropometric markers when compared to those exposed to single dose, short course zidovudine. The HAART exposed infants had lower birth weights but weight had caught up by 3 months of age, while lower average length persisted for the first 6 months of life [12].

Other African studies have also examined growth among HEU infants, with many studies conducted prior to the introduction of prophylactic antiretroviral therapy.

A prospective cohort study conducted in The Democratic Republic of Congo (1989-1992) among infected and uninfected mothers [13] examined growth amongst infants by maternal and infant HIV status. Similar to the two Botswana studies, HEU infants had lower birth weights compared to unexposed infants and by 3 months of age, HEU infants had similar anthropometric profiles compared to unexposed infants. This trend continued until aged 20 months when follow up ceased. A prospective Rwandan study over the same time period (1988-1993) found that both the mean z-score for weight-for-age and height-for-age amongt HEU infants were statistically significantly lower when compared to unexposed infants at 6 months of age. Height-for-age and weight-for-age were then comparable from 9 months of age through to 48 months [14].The ZVITAMBO (Zimbabwe Vitamin A for Mothers and

Babies Project) study conducted in Zimbabwe (1997-2000) also found that HEU infants had significantly lower birth weights when compared to unexposed infants [15].

A Zambian study investigating early growth (until 16 weeks of age) of infected and uninfected infants (2001-2003) found that infants of infected mothers had lower weight-for-age and length-for-age z-scores at 6 and 16 weeks when compared to uninfected mothers. This difference was only statistically significant for weight at 6 weeks of age. A major limitation of this particular study is that infant HIV status was unknown. The study authors had attempted to overcome this shortfall by limiting the analysis to infants who were still alive and assumed HIV-free between the ages of 2 – 4 years [16].

These African studies contrast the European Collaborative Study (1987-2001) where children were followed-up to the age of 10 years. This study found no major differences in growth between HEU children and children in the 1990 British growth standards [17].

Infant feeding options and growth

In a study examining growth faltering following breastfeeding cessation among HEU infants, it was found that an absence of breastfeeding was associated with significant decreases in weight-for-age z-scores after adjusting for possible confounders [18]. In this study among Zambian women, nearly 40% of HEU infants experienced moderate-to-severe malnutrition by the age of 2 years. Arpadi et al also found declines in length compared to WHO growth standards [18]. In a review on patterns of postnatal growth in both HIV-infected and uninfected exposed children, the authors concluded that the difference in early growth of HEU compared to healthy controls was small but also that data on growth beyond 2 years of age was limited and that follow-up periods may not be of adequate length to fully capture changes in growth patterns [19].

A Kenyan study looking at the outcomes of HEU infants and the efficacy of PMTCT in a resource-constrained setting found that in children with documented feeding modality, there was no difference in the combined endpoint of HIV infection or death by feeding mode [20]. Moreover, formula feeding did not confer a benefit at 18 months of age (when compared to breastfeeding). Among HIV-infected mothers who received prophylactic ART, there was a significant reduction in HIV infection and death of their infants at both 3 and 18 months of age [20].

It is therefore clear that although breastfeeding does confer a risk of transmission of HIV, the use of ARVs in both mothers and their infants can help stem this. Furthermore, there are other benefits of breastfeeding that formula feeding cannot confer, especially when one considers protection against infectious diseases including acute respiratory tract infections and diarrhoea [21].

Despite the short-term nature of studies examining the effects of extended exposure to antiretroviral drugs, HEU infants can evidently benefit from prophylactic use. Knowledge of the characteristics of these infants has the ability to provide guidance to the type of healthcare they will require in the long term. It will also assist in providing improved care to HIV-infected mothers to ensure their infants are born, and remain, uninfected in spite of their exposure status.

2. Justification

As mentioned previously, HEU infants are frequently overlooked and this study will provide information on their characteristics, specifically in a Southern African context.

This study will describe a cohort of HIV-exposed uninfected infants within the International Epidemiological Databases to Evaluate AIDS Southern Africa (IeDEA-SA) network.

Furthermore, the growth outcomes of these infants during their first 2 years of life will be examined.

3. Objectives

Primary

1. To describe the cohort of HEU infants within the IeDEA-SA network. This will include gender, weight and height classification according to the WHO z-scores, anthropometric measures at birth and follow-up visits, gestational age, feeding modality, opportunistic infections and social variables such as the primary care giver. The antenatal and postnatal exposure of ARVs of both the mother and the infant will also be described.
2. To examine growth outcomes among HEU infants during the first 2 years of life
3. To compare effects of different ARV exposures of HEU on infant growth

III. Methodology

1. Study design

This will be a retrospective cohort analysis of data from HIV-exposed uninfected infants being followed up at collaborating IeDEA Southern Africa sites

Study population

All collaborating IeDEA-SA sites will be invited to contribute data to the analysis (two South African sites and one in and Mozambique).

The IeDEA-SA cohort profile has been described elsewhere [22, 23].

Table 1 contains a brief description of the sites that will be contributing to this study.

Table 1 Summary of contributing IeDEA-SA sites

Site	Setting	No. of HEU infants	Follow-up period
Rahima Moosa Mother and Child Hospital	Johannesburg, South Africa; urban	6000	2500 with at least 1 visit
Centro de Investigaçao em Saude de Manhiça (CISM)	Manhica, Mozambique; rural	496	12 months
McCord Hospital	Durban, South Africa; urban	802	18 months

The sites all collect baseline variables including date of birth, birth anthropometry and intended feeding method. PMTCT information is collected for both mother and infant. Feeding and anthropometry are assessed per visit. McCord Hospital and Rahima Moosa Mother and Child Hospital collect additional information including source of income and employment as well as whether or not the pregnancy was planned.

2. Research procedures and data collection methods

Permission will be obtained from collaborating IeDEA-SA sites to utilise data on HEU infants in the analysis. The data, although held at the University of Cape Town, belongs to the individual sites and thus permission will be needed before analysis can commence. All sites have existing ethical approval from their respective institutional Research Ethics Committees to contribute data to IeDEA-SA Collaborative analyses.

Sample size will not be calculated but all infants from participating sites who are exposed but uninfected will be included in the analysis.

The data that will be used for analysis are anonymised prior to importing into the IeDEA database and any identifying information is held at the individual sites.

Inclusion and exclusion criteria

Although the aim is to include all HEU infants from participating sites, this may not be possible due to missing variables.

The exclusion criteria will thus exclude infants who have an unknown HIV status at first visit.

This study will be limited to those where the pregnancy history, including ARV exposure, is known. In addition, the infants will need to have been followed up from birth.

IV. Measurement

1. Instrument

The individual contributing sites within the IeDEA-SA network collect routine data. This data is stored within electronic databases or as paper records. A data transfer protocol (DTF) has been developed to import data from each site to the database based at the University of Cape Town. The DTF was updated to include the capturing of information on HEU infants (Addendum A). The following tables in Addendum A are of particular importance for HEU infants: tables 1.1, 1.3, 2, 3, 5.1, 5.2, 6, 7, 8 and 9.

2. Variables

Table 2 lists some of the variables included in the data transfer protocol.

Table 2 Summary of list of variables

Variable Name	Type of Variable
Date of birth	Numerical
Gender	Binary
Weight, height, head circumference, mid-upper arm circumference	Numerical
Gestational age	Numerical
Feeding modality	Nominal
Opportunistic infections	Nominal
Social variables e.g. caregiver	Nominal
ARV exposure (mother and infant)	Nominal

The exhaustive list of individual variables can be found within the data transfer protocol in addendum A.

The outcomes will be the WHO weight-for-age, height-for-age and weight-for-height z-scores at 1 and 2 years of age as well as the HIV transmission rate over 2 years.

3. Validity and reliability of measuring instruments

The DTF protocol is based on the HICDEP (HIV Cohorts Data Exchange Protocol, see http://www.hicdep.org/) and has been utilised for transfer of data of infected adults and children. Additional variables have been included for HEU infants.

V. Data analysis plan

1. Data analysis

The data analysis will be of pooled retrospective data from the IeDEA-SA cohorts using the agreed format for HEU infants. The statistical package- Stata v12.0 will be used to perform the analysis.

Characteristics of HEU infants that will be described include weight and height z-scores, ARV exposure history and feeding modalities. Continuous variables will be summarised using means/medians and categorical variables with proportions.

Feeding modes will be described, as far as possible, using the WHO feeding criteria [24, 25].

Table 3 WHO definitions of infant feeding modes

Term	Definition
Exclusive breastfeeding (EBF)	Giving the infant breast milk only (including expressed breast milk), and drops or syrups consisting of vitamins, mineral supplements or prescribed medicines if required.
Predominant breastfeeding (PrBF)	The predominant source of nutrition for the infant is breast milk. However, the infant may also receive water or water-based drinks; fruit juice; oral rehydration salts; drop and syrup form vitamins, minerals and medicines; and folk liquids (liquids used for non-nutritional purposes e.g. tea for relief of colic). With the exception of fruit juice and sugar water, no food-based fluid is allowed under this definition
Partial breastfeeding (PaBF)	Giving a baby some breastfeeds, some artificial feeds, either milk or cereal or other food
Mixed feeding (MF)	Giving a baby both breast milk and other foods or liquids, including water (i.e. includes predominant and partial breastfeeding)
Exclusive formula feeding (EFF)	Giving the infant only commercial infant formula for the first six months of life

Linear and/or logistic regression models will be utilised to determine differences in growth outcomes among HEU infants by the different types of ARV antenatal exposure and prophylaxis (of both mother and infant) as well as by differences in feeding modality.

Table 4 Dummy table - HEU infant characteristics

Characteristics	Overall	By sex		Per study site		
		M	F	A	B	C
% male		-	-			
% female		-	-			
Median (IQR) gestational age						
Median (IQR) birth weight						
Median (IQR) birth length						
Median (IQR) birth head circumference						
Median(IQR) WHO weight-for-age z-score						
Median(IQR) WHO length-for-age z-score						
Median (IQR) WHO weight-for-length z-score						
% breastfed(all definitions – 3mths)						
% breastfed (all definitions – 6mths)						
Feeding at 3 months:						
% EBF						
% PrBF						
% PaBF						
% MF						
% EFF						
Feeding at 6 months:						
% EBF						
% PrBF						
% PaBF						
% MF						
% EFF						
% Solids + BF at 1 yr						
% Solids + BF at 18mths						
% Solids + FF at 1yr						
%Solids + FF at 18mths						
Prophylaxis:						
Mother						
Regimens by infant feeding mode (%)						
Infants – regimens %						
Regimens by infant feeding mode (%)						

Table 5 Dummy table - Maternal characteristics

Characteristics	Overall	Per study site		
		A	B	C
Mean age				
Mean parity				
% intend to BF				
% intend to FF				
% feeding intention unknown				
Mean CD4 (cells/µl) during pregnancy				
Median VL during pregnancy				
Mean CD4 (cells/µl) after pregnancy				
Median VL after pregnancy				
ART				
% lifelong/ pre-pregnancy ART				
% regimens				
Prophylaxis				
% not on ART pre-pregnancy				
% commence ARVS 1st trimester				
% regimens				
% commence ARVs 2nd trimester				
% regimens				
% commence ARVs 3rd trimester				
% regimens				
% first ARVs during labour				
% regimens				
% ARVs given post delivery				
% regimens				
% ARVs postnatal				
% regimens				

Table 6 Dummy table – HEU infant outcomes

Outcomes	Overall	By sex		Per study site		
		M	F	A	B	C
1 year of age						
Median (IQR) WHO weight-for-age z-score						
Median (IQR) WHO length-for-age z-score						
Median (IQR) WHO weight-for-length z-score						
2 years of age						
Median (IQR) WHO weight-for-age z-score						
Median (IQR) WHO length-for-age z-score						
Median (IQR) weight-for-length z-score						

VI. Ethics

1. Study protocol approval

The International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration (formerly known as the Observational Antiretroviral Studies in Southern Africa [OASIS] Collaboration) has approval from the University of Cape Town Research Ethics Committee to collate anonymised routine individual patient data from HIV care and treatment programmes, including that of HIV exposed uninfected infants (HREC REF 084/2006). Each participating cohort has approval from their institutional human research ethics committee to participate in the collaboration and contribute data.

These details can be found in Appendices B and C.

2. Site participation

The contributing IeDEA-SA cohorts will provide permission to utilise their data. All sites have ethics approval to contribute data to the collaboration.

The individual sites will have received informed consent from patients if this was required by the respective institutional research ethics committee. Most of the research ethics committees felt that informed consent was not required as only routine patient data that was already being collected for monitoring and evaluation purposes was included, and all data is transferred to the IeDEA-SA Data Centre only after it has been anonymised.

3. Privacy and confidentiality

The data imported into the IeDEA database from each site is anonymised and identifying information is held at the individual sites. Thus, the privacy and confidentiality of all participating individuals is ensured.

4. Reimbursement for participation

Sites are funded and remunerated according to their contributions to the IeDEA network.

5. Risks and benefits of participation

Potential benefits

The contributing sites will be provided with the study results. As the data is anonymised there is no direct benefit to individual patients from the contributing sites. However, the sites will have the characteristics on the sub-cohort of infants who are exposed to HIV but uninfected.

The description of these infants may allow study sites to better tailor healthcare for these infants if it is within their scope of practice. Alternatively, appropriate referrals to other healthcare providers can be made.

Potential risks

There are minimal risks to those sites participating in the study. Anonymity of patients is ensured as each site keeps all identifying information. When the data are imported, it is

password protected and these passwords are made available telephonically or via facsimile only. The purpose of this study is to expand the current knowledge base of HEU infants.

6. Reporting to stakeholders

As the data is part of the IeDEA-SA cohort collaboration, the results of this study will be disseminated to all participating IeDEA-SA sites. It will be presented at appropriate academic conferences and submitted for publication in a peer-reviewed journal.

VII. Logistics

1. Timetable

Table 7 Gantt Chart - timeline of actions

Timeline	2013												2014							
Actions	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug
Finalise concept sheet																				
Circulate concept sheet within IeDEA																				
Finalise protcol																				
Finalise data transfer protocol																				
Departmental approval submission																				
Finalise contributing sites																				
Import data from sites																				
Literature review																				
Data cleaning																				
Data analysis																				
Submit to HREC (2014 updated requirements)																				
Write-up analysis																				
Final report																				
Dissemention of results																				
Submit for publication																				

2. Budget

The sites contributing to the collaboration are funded by IeDEA. No additional resources are required as this study is for the purpose of obtaining my master‘s degree.

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IX. Post-script

Mozambican data

In the final analysis the Mozambican data were not included as there were substantial delays on the part of the contributing cohort in providing data and queries that could not be resolved.

Opportunistic infections and introduction of solids

In the data provided by McCord and Rahima Moosa Mother and Child hospitals, the introduction of solids and opportunistic infections were not assessed as this data was not routinely collected.

Birth weight

Factors affecting birth weight were investigated separately from growth as birth weight was found to be an important determinant of postnatal growth.

Data analysis

Mixed effects models were used to assess growth among the HIV exposed uninfected infants. The mixed effect model was selected as it allows for fixed and random effects when looking at subjects with repeated measurements. The analysis of cohort data does not assess causality. In addition, as this analysis was based on routine data, missing data was taken into account by restricting to those with complete information or including a missing category into the regression models.

Part B: Literature review

1. Introduction

Globally, and particularly in sub-Saharan Africa, HIV-exposed uninfected (HEU) infants are a growing population. This sub-population will continue to increase in number as access to antiretroviral drugs (ARVs) continues to improve, especially within the South African prevention-of-mother-to-child transmission (PMTCT) programme that is no longer vertical but aimed to be integrated into all maternal and child health services [1]. In 2010, The World Health Organization (WHO) introduced Option B, combination antiretroviral therapy (ART) for the duration of pregnancy and breastfeeding with lifelong ART for women with a CD4 count of <350 cells/μl [2] . Malawi modified this to Option B+, lifelong ART for all pregnant and breastfeeding women, irrespective of CD4 cell count. Countries are increasingly adopting Option B+ for their PMTCT programmes [3]. Consequently, more infants will be exposed to triple therapy *in utero* and during breastfeeding, thus a further increase in the numbers of infants who are exposed yet uninfected is likely to occur.

In South Africa, the prevalence of HIV among pregnant women in 2011 was 29.5% [4] and remained steady in 2012 [5]. Across the public and private healthcare sector approximately 87% of all HIV-infected pregnant women in South Africa received ARVs for the purposes of PMTCT in 2011 [6]. An evaluation of the effectiveness of the PMTCT programme was conducted in 2010 by the Medical Research Council (MRC) of South Africa. This cross-sectional, facility-based survey examined, inter alia, early HIV transmission rates (4-8 weeks postpartum) among exposed infants. Overall, the early transmission rate of HIV was 3.5% (variable across the nine provinces) and infection prevalence was 1.5%, thus, by 8 weeks of age, the majority of infants are exposed yet uninfected [7].

The focus of this literature review will be on these HEU infants, with particular focus on the infant feeding method and its effect on growth.

1.1 Objectives

The aim of this literature review is to appraise published studies, including observational studies, randomised controlled trials, and meta-analyses where HEU infants were included as subjects. It is only with the success of PMTCT programmes that the sole focus was diverted from HIV-infected infants, and included HEU infants. Thus, studies solely investigating HEU infants, particularly historically, are relatively uncommon.

The objectives of this review are to investigate the following, focussing on Africa:

- The effect of HIV exposure, maternal HIV clinical stage and the maternal and infant exposure to antiretroviral drugs in conjunction with the effect of feeding modality on the postnatal growth of uninfected infants.
- The differences in postnatal growth outcomes based on infant feeding modality.

HIV exposure *in utero* and perinatally has multiple possible effects on exposed infants including the risk of acquiring HIV and an increased risk for other infection [8]. As this review has a particular focus on growth and feeding, other outcomes in HEU infants such as HIV transmission, infectious disease morbidity and mortality will not be discussed but they are acknowledged. Infant feeding, particularly breastfeeding, not only impacts nutritional status and growth, but infectious diseases and mortality too [9]. Owing to this interaction, and the known transmission of HIV via breastfeeding [10], studies examining morbidity (including HIV transmission) and mortality were also reviewed. An understanding of factors increasing the risk of HIV transmission is important to minimise infection and increase the number of infants who remain uninfected, despite HIV exposure.

There are key contextual differences between developed and developing countries, including access to, and guidelines on the use of, antiretroviral drugs (ARVs) and infant milk formulae. These differences are reflected in the differing practices (and their impact on health

outcomes) between developed and developing countries, especially when looking at infant feeding modes [11, 12].

1.2 Search strategy

PubMed (US National Library of Medicine, National Institutes of Health) was used to search the Medline database. A combination of Medical Subject Headings (MeSH terms) and key words were used when searching PubMed. The search terms are as follows:

- ((feeding[All Fields] AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]))
- (("breastfeeding"[MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breastfeeding"[All Fields] OR "breastfeeding"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]))
- (feeding[All Fields] AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND exposed[All Fields] AND uninfected[All Fields])
- (("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND exposed[All Fields] AND uninfected[All Fields] AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields]))
- (("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND exposed[All Fields] AND uninfected[All Fields] AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields]) AND ("growth and development"[Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms]))
- (("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND exposed[All Fields] AND uninfected[All Fields] AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields]) AND ("growth and development"[Subheading] OR ("growth"[All

Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms]))

- ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND exposed[All Fields] AND uninfected[All Fields])

There was some overlap in the articles found based on the above search strategy but it yielded articles looking at HIV and feeding modality, and the growth and development of HEU infants. I set up monthly updates from PubMed using the same search terms, and set up a Google Scholar alert for new articles on HEU infants.

The alerts were set up as follows:

- [intitle:"hiv exposed uninfected infants"]
- [intitle:"hiv exposed uninfected" infants growth]

In addition to this strategy, I used the reference list of numerous articles found as a further source for articles on HEU infants, particularly since HEU infants have only recently been studied as primary subjects. Earlier studies looking at HIV infection and PMTCT among infants mention HEU infants, but they were often not the focal point of the study. The search for articles for this review was conducted periodically between June 2012 and September 2013. Thereafter, the monthly updates and alerts were reviewed and articles included as appropriate. For the purposes of this review, articles found through to December 2013 were assessed.

Studies were included if HEU infants were part of the analyses. In addition, selected studies needed to have examined growth and/or included information on feeding method as well as have conducted an analysis of the effect of feeding on growth (and/or mortality and morbidity) and not merely provided descriptive statistics. Studies from African countries were included. Studies were excluded if HIV-infected infants were the only subjects. Furthermore, studies looking only at the efficacy of antiretroviral drugs or their toxicity were excluded.

However, efficacy trials with a feeding component were included, as breastfeeding is known to increase the risk of transmission and it is important to consider the extent to which use of ARVs mitigates this risk [10].

2. Characteristics of studies

Twenty-four publications met the inclusion criteria, with three studies resulting in more than one publication from the same primary study, but with a different outcome. Fifteen publications were on results from randomised controlled trials, six on results from observational studies, and three were meta-analyses.

The characteristics of studies included in this literature review are described in tables 1 through 4. Tables 1 and 2 cover randomised controlled trials, while tables 3 and 4 summarise observational studies and meta-analyses, respectively. These characteristics reflect study quality and comparability. The study characteristics are intended to provide a brief background to each study and the context in which they occurred. Minor differences in studies influence their comparability. For instance, the criteria for the use of ART, for pregnant women was initially a CD4 cell count of ≤200 cells/µl, increasing to ≤ 350cells/µl [2] and with the latest WHO consolidated guidelines stating that all pregnant HIV-infected women should receive ART [13]. Similarly, the availability and use of ARVs changed over time for both mothers and infants. Changing one factor, e.g. infant prophylaxis for varying durations or doses, will reduce comparability of studies.

Tables 5 to 7 contain additional details reflecting the quality of the studies including sample size, ARV use and feeding method together with how feeding modality was defined. These quality measures will impact the interpretation of the study results. Sample sizes influence the magnitude of effects as well as the size of confidence intervals. This is particularly important when looking at groupings of outcomes or feeding modality.

Table 1 Study details: randomised controlled trials

Authors	Country	Additional study details
Thior et al 2006 [14]	Botswana, Mashi Study	RCT with 2X2 design, comparing interventions to prevent perinatal transmission (part 1) and reduce postnatal HIV infection and mortality (part 2). Part 1 investigated the efficacy of adding sdNVP to maternal and infant ZDV to reduce perinatal MTCT. Part 2 was randomised, unblinded and looked at the efficacy of ARVs per feeding modality. Mothers were randomised into: i) BF plus infant ZDV for 6 months ii) FF plus infant ZDV for 1 month
Kuhn et al 2005 [15] Kuhn et al 2007 [16] Kuhn et al 2009 [17] Arpadi et al 2009 [18] Kuhn et al 2010 [19]	Zambia Exclusive Breastfeeding study (ZEBS)	RCT investigating early cessation of breastfeeding. All women were counselled to breastfeed exclusively through to 4 months of age. Women were then randomised into: i) Abrupt cessation BF at 4 months (intervention) ii) Continued EBF, with gradual weaning until 6 months (control) Analysis restricted to HEU infants still BF by 4months. Arpadi et al (2009) evaluated the effect of timing of BF cessation on growth among HEU.
Coutsoudis et al 2001 [20]	South Africa, Vitamin A Study	RCT investigating vitamin A to reduce MTCT of HIV. Pregnant women were randomised into: i) Vitamin A ii) Placebo Mothers were counselled on transmission risk with BF as well as the health benefits of BF, infant feeding was based on mother‘s informed choice.
Nduati et al 2000 [21] Mbori-Ngacha et al 2001 [22] McGrath et al 2012 [23]	Kenya, Breastfeeding and transmission of HIV study	Pregnant women were randomised into: i) Breastfeeding ii) Formula feeding
Illiff et al 2005 [24]	Zimbabwe Vitamin A for Mothers and Babies Project (ZVITAMBO)	Aim: measure effect of single dose postpartum vitamin A supplementation on maternal and neonatal health outcomes (4 vitamin A groups, within 96 hours of delivery) Secondary objective: investigate breastfeeding associated infant feeding practices and the role in HIV transmission
Muhangi et al 2013 [25]	Uganda	Trial of anthelminthics in pregnancy, 2x2 factorial design i) Albendazole vs. placebo ii) Praziquantel vs. placebo Retrospective analysis was conducted looking at differences in growth at 12months of age between HEU and HIV-unexposed infants

Authors	Country	Additional study details
Taha et al 2011 [26, 27]	Malawi, PEPI-Malawi	A randomised, controlled, open-label phase 3 clinical trial. Infants were randomised into 3 arms: i) Control: oral sdNVP at birth and twice daily for 1 week ii) Control regimen + extended daily NVP until age 14 weeks iii) Control regimen + extended daily NVP and ZDV until age 14 weeks
Homsy et al 2010 [28]	Uganda	RCT evaluating clinical and laboratory based strategies for monitoring ARV therapy with an MTCT sub-study.
Natchu et al 2012 [29]	Tanzania, Trial of Vitamins	Aim: Examine the effects of oral supplementation of multivitamins on disease progression in mothers, MTCT and mortality and morbidity outcomes in mothers and infants

sdNVP: single dose nevirapine; ZDV: zidovudine; 3TC: lamivudine; BF: breastfed; EBF: exclusive breastfeeding; FF: formula fed

Table 2 Characteristics of randomised controlled trials

Authors	Study details Country & time	Inclusion criteria Mother	Infant	Exclusion criteria
Thior et al 2006 [14]	Botswana 2001-2003 Mashi study	≥18years of age 33-35 weeks gestation HIV-infected Hb ≥80g/L; absolute neutrophil count ≥1000 cells/mm; no intolerance to ZDV & NVP		
Kuhn et al 2009 [17]	Lusaka, Zambia 2001-2004 (ZEBS)	*Kuhn '09:* Analysis restricted to 661 mother-infants pairs where infants remained uninfected and were still BF at 4 months.		
Kuhn et al 2007 [16]		*Kuhn '07:* Nested observational cohort study within RCT comparing effects of EBF and non-EBF on the risk of post-natal HIV transmission	*Kuhn '07:* 743 infants HIV-free to 6 weeks and still BF at 4 months	
Kuhn et al 2010 [19]		*Kuhn '10:* 749 uninfected infants at last PCR – looking at effect of weaning at different ages on mortality	*Kuhn '10:* 749 uninfected infants at last PCR	
Kuhn et al 2005 [15]		*Kuhn '05* Restricted to mothers who gave birth to live-born infants before December 2003		
Arpadi et al 2009 [18]			*Arpadi'09:* 595 HEU live singleton births	*Arpadi '09:* In this analysis, if breastfed <120 days were excluded & infants LTFU/died before 150 days were excluded to minimise attrition during the weaning period for the intervention group
Coutsoudis et al 2001 [20]	Durban, South Africa 1995-1998 South African Vitamin A study	HIV-infected mothers were recruited from antenatal clinics for Vitamin A trial and chose feeding method based on informed choice. Dependent on choice, mothers were counselled appropriately and feeding choice supported. Formula had to be purchased at a subsidised rate.		

Authors	Study details Country & time	Inclusion criteria Mother	Infant	Exclusion criteria
Nduati et al 2000 [21]	Nairobi, Kenya. 1992-1998 Breastfeeding and Transmission of HIV study	HIV-infected mothers residing in Nairobi, with access to municipal treated water. Mothers had to agree to mode of feeding as randomised prior to enrolment. At 32 weeks gestation women were randomised into either BF or FF arms. Formula was provided free of charge.	Live-born singleton & first-born twins included in analysis	
Mbori-Ngacha et al 2001 [22]		*Mbori-Ngacha'01*: focus on morbidity and mortality between BF & FF infants.		
McGrath et al 2012 [23]		*McGrath'12*: prevalence of stunting – looked at ITT & PP analysis.		*McGrath '12:* Infants testing HIV positive at birth and infants with no follow-up information after birth
Illiff et al 2005 [24]	Harare, Zimbabwe 1997-2000 (ZVITAMBO)	Mother-infant pairs were eligible if neither had a life-threatening condition and planned to stay in Harare after delivery. Mothers had to be HIV-infected at delivery.	Birth weight ≥ 1500g, singleton Infants had to be PCR negative at 6 weeks and have feeding information available at birth, 6 weeks and 3 months.	
Muhangi et al 2013 [25]	Uganda 2003-2005	Pregnant women eligible if they were well, resident in Entebbe, planned to deliver at the hospital, willing to participate and know HIV status		Pregnant women excluded if Hb<8g/dl, clinically apparent liver disease, bloody diarrhoea, abnormal pregnancy, history of adverse reactions to antihelminthics

Authors	Study details Country & time	Inclusion criteria Mother	Infant	Exclusion criteria
Taha et al 2011 [26]	Malawi 2004-2009 PEPI-Malawi	HIV-infected pregnant women (or had delivered within the previous 24 hours), ≥18 years of age (if <18 years, guardian permission) receiving antenatal care or who delivered at one of the 5 study healthcare facilities. Mothers had to be resident in the area, willing to return for postnatal follow-up up to 2 years and intend to BF [27].	In this analysis included if BF at 14 weeks and HEU at 6 months of age	Infants with life-threatening conditions
Homsy et al 2010 [28]	Uganda 2003-2007	All HIV-infected female index clients who delivered one or more live infants were enrolled.		
Natchu et al 2012 [29]	Tanzania 1995-1997 Trial of Vitamins	HIV-infected pregnant women between 12 and 27 weeks gestation	Infants included in analysis if uninfected at birth	Infants were excluded if HIV-infected at birth/first visit, no follow up visit before 2yrs of age, unable to determine EBF duration, died within 1 month of stopping EBF and if HIV status was unknown.

BF: breastfed; EBF: exclusive breastfeeding; FF: formula fed; NVP: nevirapine; ZDV: zidovudine; ITT: intention-to-treat; PP: per protocol

Table 3 Characteristics of observational studies

Authors	Study details Country & time	Inclusion criteria Mother	Infant	Exclusion criteria
Landes et al 2012[30]	Retrospective cohort , Malawi 2008-2009	HIV infected mothers who attended facilities in the region with due date between 1 March – 31 May 2008 For every HIV-infected mother identified in the register, the next uninfected mother was selected as a control		
Bobat et al 1997[31]	Prospective cohort, South Africa 1990-1993	Criteria not stated	Live-born infants of HIV-infected mothers	
Coovadia et al 2007 [32]	Non-randomised intervention cohort, South Africa 2001-2004 Vertical Transmission study (VTS)	HIV infected & uninfected mothers attending antenatal clinics in KZN, >16 years of age, planned to stay in study area for at least 3 months after delivery & gave written consent. Feeding choice was supported by counsellors doing home visits (whether antenatal choice or present choice). This analysis was restricted to HIV infected mothers.		
Patel et al 2010 [33]		*Patel'10:* For this analysis, maternal HIV had to be known	*Patel'10*: Children had to have a gestational age between 18 and 45 weeks and at least 1 measurement at birth.	*Patel'10*: For the reference infant population (born to uninfected mothers), infants were excluded if weighed <2500g and were preterm and observations ± 4SD of sample median were excluded
Makasa et al 2007 [34]	Longitudinal cohort study, Zambia 2001-2003	Pregnant women (32-34weeks gestation) who resided in Chilenje clinic catchment, known HIV status, intention to BF & signed informed consent		
Goga et al 2012 [35]	Prospective observational cohort , South Africa 2002-2003	Consecutive HIV positive & negative women were enrolled 3:1 and followed up until 36 weeks postpartum		

BF: breastfed; EBF: exclusive breastfeeding; FF: formula fed; NVP: nevirapine; ZDV: zidovudine

Table 4 Characteristics of meta-analyses

Authors	Study details Country & time	Inclusion criteria Mother	Infant	Exclusion criteria
RCTs				
Taha et al 2010 [36]	Malawi NVAZ trials 2000-2003	HIV infected women were enrolled after obtaining informed consent.	Infants were included for this analysis if they returned for follow-up visit at 6-8 weeks.	
Newell et al 2004 [37]	7 trials conducted in SSA Split geographically in analysis: east Africa (Tanzania & Kenya), west Africa (Côte d'Ivoire)& South Africa SA Vitamin A study** Chlorhexidine Intervention study RETRO-CI study ANRS049a& b Mother-Baby study** PETRA	Criteria not stated		
Observational				
Becquet al 2009 [38]	2 cohorts: Vertical transmission study**, South Africa Ditrame Plus ,Côte d'Ivoire VTS 2001-2004 Ditrame Plus 2001-2003	Ditrame Plus: HIV infected women ≥18 years VTS: HIV infected women ≥16 years	In this analysis breastfed infants who were HIV uninfected at or after 30 days included.	

**Studies included in this literature review; SSA: sub-Saharan Africa

Table 5 Quality measures: randomised controlled trials

Authors	Follow-up	Sample size	Feeding Methods &definition		ARVs Mothers Yes/No + regimens	Infants Yes/No + regimens
Thior et al 2006 [14]	18 months	591 FF 588 BF	EBF MBF PrBF EFF	BF only, no other fluids or food BF + other fluids, solid foods & non-human milk BF + other fluids, excl milk FF only, never BF	ZDV: 34 weeks gestation to deliver & sdNVP	ZDV until 1 month for all infants. Continued to 6 months if infants BF.
Kuhn et al 2009 [17] Kuhn et al 2005 [15] Kuhn et al 2007 [16] Kuhn et al 2010 [19] Arpadi et al 2009 [18]	24 months	*'09*: 661 dyads, still BF at 4mths infants *'05*: 620 HEU infants (f/up until 4/12) *'07*:734 infants HIV-free to 6 weeks & still BF at 4mths *'10*:958 dyads, 749 with last PCR negative *Arpadi '09*: 593 HEU	EBF	EBF until 4/12, only BM no other foods or liquids	sdNVP	sdNVP
Coutsoudis et al 2001 [20]	15 months	551 dyads	Informed choice BF -394 FF – 157	Ever BF including EBF (EBF for ≥ 3months) and MBF (EBF < 3 months or no EBF) FF: never BF	No	No
Nduati et al 2000 [21] Mbori-Ngacha et al 2001 [22] McGrath et al 2012 [23]	24 months	401 dyads	FF-204 BF-197	FF: complete avoidance of BM BF: any use of BM	No	No

Authors	Follow-up	Sample size	Feeding Methods &definition		ARVs Mothers Yes/No + regimens	Infants Yes/No + regimens
Illiff et al 2005 [24]	18 months	2060 infants	EBF	Only BM, no other liquids, milks or solid foods	No	No
			PrBF	BM predominant source, but non-milk liquids were also given		
			MBF	BM, non-human milk, and solid or semi-solid food.		
Muhangi et al 2013 [25]	18 months	1502 infants 1380 unexposed 122 HEU	BF	Looked at early weaning – defined as introduction of cow's milk before 6 weeks of age	sdNVP	sdNVP
Taha et al 2011 [26]	24 months	3 age groups: 6-9mths: 1761 9-12mths: 1633 12-15mths: 1543	BF NBF	Breastfeeding Non-breastfeeding	sdNVP; HAART became available (131 mothers started during the follow-up period)	sdNVP & bd ZDV: 1 week (control) NVP for 14 weeks + control NVP & ZDV for 14 weeks + control
Homsy et al 2010 [28]	18 months (median)	118 infants	EBF	Only BM	HAART: 3TC, D4T & NVP	sdNVP/ZDV added 2005
Natchu et al 2012 [29]	60 months	585 infants	EBF	BM only, without any other liquid, milk or solids	No	No

sdNVP: single dose nevirapine; NVP: nevirapine ZDV: zidovudine; 3TC: lamivudine; D4T: stavudine; HAART: highly active antiretroviral therapy; mths: months; bd: twice daily

BF: breastfeeding, BM: breast milk, EBF: exclusive breastfeeding, MBF: mixed breastfeeding, PaBF: partial breastfeeding, PrBF: predominant breastfeeding, FF: fofmula feeding, EFF: exclusive formula feeding

Table 6 Quality measures: observational studies

Authors	Follow-up	Sample size	Feeding Methods & definition		ARVs Mothers Yes/No + regimens	ARVs Infants Yes/No + regimens
Landes et al 2012[30]	18-20 months	173 HIV-infected mothers 214 uninfected mothers	BF/MBF	Definitions not provided	sdNVP/ART	sdNVP
Bobat et al 1997[31]	2924 child-months follow up	93 HEU infants 48 HIV-infected infants 40 indeterminate	Self-selected EBF MBF FF	 Only BM from birth Both FF & BM FF only	No	No
Coovadia et al 2007 [32]	*Coovadia* 26 weeks	1276 HIV-exposed infants with 6 months complete feeding history	Self-selected EBF MBF	 Only BM from birth, no other liquids or solids BM & non-human milk, other liquids or solids	sdNVP	sdNVP
Patel et al 2010 [33]	*Patel* 24 months	*Patel'10:* 910 HIV-exposed infants with anthropometric measures	FF	Non-human milk, exclusion of BM, with or without other liquids or solids		
Makasa et al 2007 [34]	2-4 years Early growth assessed (birth, 6wks and 16 weeks)	85 infants of HIV-infected mothers who appeared uninfected 184 infants of HIV-uninfected mothers	BF	EBF only BM from birth	sdNVP	sdNVP

Authors	Follow-up	Sample size	Feeding Methods & definition		ARVs Mothers Yes/No + regimens	Infants Yes/No + regimens
Goga et al 2012 [35]	36 weeks	665 HIV-infected mothers & infants 218 HIV-uninfected mothers & infants	EBF MBF EFF MFF	BM only, prescribed medication allowed BM and/or FF and other foods (solids/liquids) FF only FF and other foods (solids/liquids) were provided	sdNVP	sdNVP

sdNVP: single dose nevirapine; mths: months

BF: breastfeeding, BM: breast milk, EBF: exclusive breastfeeding, MBF: mixed breastfeeding, PaBF: partial breastfeeding, PrBF: predominant breastfeeding, FF: fofmula feeding, EFF: exclusive formula feeding, MFF: mixed formula feeding

Table 7 Quality measures: meta- analyses

Authors	Follow-up	Sample size	Feeding Methods & definition		ARVs Mothers Yes/No + regimens	Infants Yes/No + regimens
RCTs						
Taha et al 2010 [36]	24 months	1589 infants	BF	Classified as yes or no at each visit	sdNVP/ZDV	No
Newell et al 2004 [37]	-	3468 infants	Ever BF Never BF	-	No	No
Observational						
Becquet al 2009 [38]	24 months	VTS 871 dyads Ditrame Plus 324 dyads	EBF EFF	BM only, prescribed medication allowed FF only	VTS: sdNVP Ditrame Plus: sdNVP& ZDV ± 3TC	sdNVP

sdNVP: single dose nevirapine; NVP: nevirapine ZDV: zidovudine; 3TC: lamivudine; mths: months

BF: breastfeeding, BM: breast milk, EBF: exclusive breastfeeding, MBF: mixed breastfeeding, PaBF: partial breastfeeding, PrBF: predominant breastfeeding, FF: fofmula feeding, EFF: exclusive formula feeding

2.1 Study design

Design

Randomised controlled trials, observational studies and meta-analyses were included in this literature review. Randomised controlled trials mostly aimed to investigate the efficacy of ARVs for PMTCT while in earlier research the risks associated with different feeding modalities in the absence of ARVs were assessed. As the importance of exclusive breastfeeding (EBF) as opposed to mixed feeding (MF) was realised, trials investigated feeding modality with the use of ARVs. However, adherence to assigned randomisation and not returning for follow-up is a concern. Cohort studies provide a more ‗true to life' scenario compared to trials, particularly as infant feeding is self-selected, and the realities of ARV access are brought to the fore, however confounding is almost inevitable as patients selecting a particular feeding modality are likely to differ with respect to a number of characteristics from those selecting a different feeding method. Cohort studies too, have the concern of participants not returning for follow-up. This loss to follow-up is important to consider as it introduces selection bias, thus skewing results. The meta-analyses included in this literature review have combined data from trials [36, 37] and cohort studies [38]. The meta-analyses presented here pooled and re-analysed data from different studies as opposed to just interpreting the results of different studies.

Formula feeding, with complete avoidance of breastfeeding, was adopted as the feeding method of choice for HIV exposed infants in developed countries many years ago [11]. Once this recommendation was adopted in developed countries, investigating the effects of feeding choice on HIV transmission became a challenge. Two trials, one in Kenya [21–23] and one in Botswana [14] randomised feeding modality. However, as knowledge expanded regarding virus transmission via feeding, and other related effects of not breastfeeding were considered, the nature of studies investigating infant feeding changed. Studies started to look at the effectiveness of the use of ARVs in reducing transmission of HIV during

breastfeeding [14, 21]. In the case of one of the Kenyan trials, the duration of follow-up was reduced to 6 months from 24 months approximately 1 year before the trial closed, and all mothers who were randomised to the breastfeeding arm were advised to stop breastfeeding and switch to infant formula (April 1998). It must be noted that this trial was conducted prior to the availability of ARVs. Additional characteristics of this trial, and other trials evaluated, are detailed in table 1.

The observational studies included in this literature review are all cohort studies (retrospective and prospective). The characteristics of these cohort studies are described in table 2.

Length of follow-up

The majority of studies in this review, whether a trial, cohort study or meta-analyses have follow-up periods of 18 to 24 months [14–19, 21–26, 28, 30, 33, 34, 36, 38]. Two cohort studies had a follow-up duration of less than 1 year [32, 35] and one study, a trial, had a follow-up duration through to 5 years of age, although the analysis included was a secondary analysis focussing on mortality risk of infants during the first 6 months of life [29].

Availability of ARVs

Seven studies were conducted prior to the availability of ARVs – whether as prophylaxis or triple therapy [20–24, 29, 37, 39]. Eight studies only had ARVs available as prophylaxis [14–19, 25, 32–36, 38] and all remaining studies (n=3) used a combination of prophylaxis and triple therapy as triple therapy became available [26, 28, 30].

2.2 Sample size

The sample sizes ranged from 93 [31] to over 2 000 HEU infants [24, 37]. However, the definition of when they were considered HEU differed across studies as not all studies had

PCR testing available to confirm HIV status. One study did not have ethical approval to test infant HIV status so they assumed infants were uninfected if still alive at 2 years of age [34]. It is possible that HIV infected infants survived to 2 years of age without showing symptoms of HIV infection, thus growth (only growth through to 16 weeks was assessed) in the HEU infants in this study population may have been underestimated, as HIV infected infants could have been included in this group.

This difference in sample size, and testing infants to confirm HIV status reflects the difficulty in studying these infants. The change in studies over time, reflecting availability of testing methods and increased knowledge on HIV transmission and the use of ARVs, also illustrates this difficulty.

3. Results from studies

The results from the studies included in this review are detailed in tables 8 through 10 for trials, observational studies and meta-analyses respectively. Where these tables report measures of association, the second variable is the reference category unless otherwise specified. Some trials analysed results based on a cohort or included a nested cohort. As these studies were originally designed as randomised control trials, their results are included in table 8. The results about feeding, growth, transmission and morbidity are discussed in detail below.

Table 8 Results from randomised controlled trials

Authors	Outcome	Comparison	Measure of Association	95% CI (p-value)	CI ratio (difference)*
Thior et al 2006 [14]	HIV transmission	BF vs. FF	1.65[#]	1.07, 2.55 (0.02)	2.38
Kuhn et al 2005 [15]	Mortality	Maternal CD4 < 350 cells/µl vs. CD4 ≥ 350 cells/ µl	2.87[#]	1.03, 8.03	7.96
		Maternal death <4 months	6.84[#]	2.65, 17.70	6.68
		Birth weight < 2500g	2.43[#]	1.05, 5.65	5.38
	Hospitalisation	Maternal CD4 < 350 cells/ µl	2.28[#]	1.17, 4.45	3.80
		Cessation BF < 4 months	3.41[#]	1.01, 11.52	11.41
	Weight (kg);1 week – 4 months	Birth weight (per 100g increase)	0.091[‡]	0.08, 0.10	0.02
		Maternal death < 4months	-0.540[‡]	-0.89, -0.19	0.70
		Not BF vs. BF	-0.252[‡]	-0.35, -0.16	0.19
Kuhn et al 2007 [16]	HIV transmission	Non-EBF vs. EBF	2.68[#]	1.27, 5.62	4.43
		Maternal CD4 < 350 cells/ µl vs. CD4 ≥ 350 cells/ µl	3.19[#]	1.19, 8.55	7.18
		Birth weight < 2500g	1.14[#]	0.46, 2.81	6.11
Kuhn et al 2009 [17]	HIV infection or death	*Within Intervention group (adherent)*			
		Less severe maternal disease vs. advanced disease	2.40[#]	1.04, 5.54 (0.035)	5.33
	HIV transmission		1.38[#]	0.34, 5.51 (0.68)	16.21
Kuhn et al 2010 [19]	Mortality	*Intervention:*			
		BF cessation	3.19[#]	1.15, 8.83	7.68
		Maternal CD4 > 350cells/µl	4.16[#]	1.90, 9.13	4.81
		Control:			
		BF cessation	2.84[#]	1.38, 5.83	4.22
Arpadi et al 2009 [18]	WAZ (4mths – 15mths)	BF cessation	-0.28[‡]	-0.39, -0.17	0.22
		High maternal VL (≥100 000 copies/ml)	-0.28[‡]	-	s.e. 0.1098
		Birth weight < 2500g	-0.87[‡]	-	s.e. 0.1475
Coutsoudis et al 2001 [20]	HIV transmission	EBF vs. MF	0.56[#]	0.22,1.42	6.45
		EBF vs. FF	0.87[#]	0.33, 2.33	7.06

Authors	Outcome	Comparison	Measure of Association	95% CI (p-value)	CI ratio (difference)*
McGrath et al 2012		*ITT analysis:*			
[23]	Underweight (WAZ)	FF vs. BF	1.05[#]	0.63, 1.77 (0.84)	2.80
		Birth WAZ per 1 unit increase	0.38[#]	0.27, 0.53 (<0.001)	1.96
	Stunting (LAZ)	FF vs. BF	1.01[#]	0.69, 1.50 (0.94)	2.17
		Birth LAZ per 1 unit increase	0.48[#]	0.40, 0.57 (<0.001)	1.43
	Wasting (WLZ)	FF vs. BF	1.34[#]	0.67, 2.68 (0.40)	4.00
		Birth WLZ per 1 unit increase	0.78[#]	0.59, 1.02 (0.07)	1.73
		PP analysis:			
	Underweight (WAZ)	Never BF vs. Ever BF	1.14[#]	0.67, 1.92 (0.64)	2.86
		Birth WAZ per 1 unit increase	0.38[#]	0.28, 0.53 (<0.001)	1.89
	Stunting (LAZ)	Never BF vs. Ever BF	0.94[#]	0.64, 1.38 (0.74)	2.15
		Birth LAZ per 1 unit increase	0.48[#]	0.41, 0.57 (<0.001)	1.39
	Wasting (WLZ)	Never BF vs. Ever BF	1.40[#]	0.71, 2.73 (0.33)	4.84
		Birth WLZ per 1 unit increase	0.78[#]	0.59, 1.02 0.07)	1.73
Illiff et al 2005 [24]	HIV transmission	*At 6 months*			
		MBF vs. EBF	4.03[#]	0.98, 16.61 (0.05)	16.95
		PrBF vs. EBF	2.63[#]	0.59, 11.67 (0.20)	19.78
		Maternal CD4 < 350cells/µl vs. CD4 >500 cells/µl	3.16[#]	1.63, 6.11 (0.0006)	3.75
		Maternal CD4 <200 cells/µl vs. CD4 > 500 cells/µl	9.12[#]	4.85, 17.13 (<0.0001)	3.53
Muhangi et al 2013	12 months of age	HEU vs. Unexposed			
[25]	Underweight <-2SD WAZ	Birth weight < 2500g	2.32[‡]	1.32, 4.09 (0.006)	3.10
		Early weaning	3.00[‡]	1.62, 5.53 (0.001)	3.41
		Maternal CD4 < 350 cells/µl vs. CD4 >350 cells/µl	1.77[‡]	1.16, 2.71 (0.010)	2.34
			3.13[‡]	0.61, 16.12 (0.169)	26.43
	Stunting < -2SD LAZ	HEU vs. Unexposed	1.55[‡]	0.92, 2.61 (0.107)	2.84
		Birth weight < 2500g	3.14[‡]	1.86, 5.29 (<0.001)	2.84
		Early weaning	1.20[‡]	0.84, 1.72 (0.314)	2.05
		Maternal CD4 < 350 cells/µl	4.09[‡]	0.64, 25.9 (0.126)	40.45
	Wasting < -2SD WLZ	HEU vs. Unexposed	0.97[‡]	0.37, 2.52 (0.947)	6.81
		Birth weight < 2500g	2.31[‡]	0.93, 5.71 (0.097)	6.13
		Early weaning	1.35[‡]	0.73, 2.50 (0.352)	3.42
		Maternal CD4 < 350 cells/µl	-	-	-

Authors	Outcome	Comparison	Measure of Association	95% CI (p-value)	CI ratio (difference)*
Taha et al 2011 [26]		Not BF vs. BF			
	WAZ ≤ 2	6-9 months	1.37¥	1.05, 1.79 (0.02)	1.70
		9-12months	1.34¥	0.97, 1.83 (0.07)	1.89
		12-15months	1.91¥	1.27. 2.89 (0.002)	2.28
	Morbidity	6-9 months	1.70¥	1.37, 2.11 (<0.0001)	1.53
		9-12months	1.66¥	1.28, 2.14 (0.0001)	1.67
		12-15months	1.75¥	1.26, 2.43 (0.0008)	1.75
	Mortality		1.78¥	1.02, 3.12 (0.04)	3.05
Homsy et al 2010 [28]	Mortality	Months of total BF (or age at weaning; continuous variable)	0.71#	0.57, 0.87 (0.001)	1.53
		BF <6 months vs. BF > 6 months	6.19#	1.41, 27.0 (0.015)	19.15
Natchu et al 2012 [29]	Mortality	EBF (time dependent variable)	0.51#	0.28, 0.93	3.32

*Confidence interval (CI) ratio or difference reflects measurement precision. The CI ratio is the UCL/LCL and is used for all logistic regression models. The CI difference is the UCL – LCL and is used for linear regression models. #Hazard ratio

ǂOdds ratio ‡linear regression coefficient ¥rate ratio s.e. standard error

Table 9 Results from observational studies

Authors	Outcome	Comparison	Measure of Association	95% CI (p-value)	CI ratio (difference)*
Landes et al 2012[30]	Mortality	HIV exposed vs. Unexposed	2.90[‡]	1.1, 7.2 (0.03)	6.55
		Birth weight < 2500g	2.50[‡]	1.0, 6.3 (0.05)	6.30
		Maternal death	5.3[‡]	1,4, 20.5 (0.02)	14.64
Bobat et al 1997 [31]	HIV transmission	EBF vs. EFF	1.63[¥]	0.71, 3.76	5.30
	Morbidity – HEU	EBF vs. EFF + MF			
	Pneumonia		1.16[¥]	0.73, 1.83	2.51
	Diarrhoea		0.76[¥]	0.48, 1.21	2.52
	Otitis media		0.97[¥]	0.32, 2.98	9.31
	Growth faltering		0.96[¥]	0.29, 3.18	10.97
Coovadia et al 2007 [32]	HIV transmission	MBF vs. EBF (HEU)	1.56[#]	0.66, 3.69 (0.308)	5.59
		In EBF infants			
		Maternal CD4 < 200 cells/µl vs. CD4 > 500 cells//µl	3.79[#]	2.35, 6.12 (<0.001)	2.60
		Birth weight < 2500g vs. > 3500g	1.81[#]	1.07, 3.06 (0.026)	2.86
Patel et al 2010 [33]	WAZ	*Exposed vs. Unexposed infants (birth weight >2500g and CD4 >500cells/µl)*			
		Birth weight < 2500g	-2.01[‡]	-2.21, -1.81 (<0.001)	0.40
		Infected vs. HEU infants	-0.20[‡]	-0.29, -0.10 (<0.001)	0.19
		Ever BF	0.048[‡]	0.011, 0.086 (0.01)	0.075
		Maternal CD4 200 -499 cells/µl	-0.15[‡]	-0.27, -0.034 (0.01)	0.236
		Maternal CD4 < 200 cells/µl	-0.32[‡]	-0.50, -0.13 (0.001)	0.37

Authors	Outcome	Comparison	Measure of Association	95% CI (p-value)	CI ratio (difference)*
Makasa et al 2007 [34]	WAZ	*6 weeks*			
		Birth WAZ	0.75‡	0.66, 0.85 (<0.001)	0.19
		16weeks			
		Birth WAZ	0.49‡	0.37, 0.60 (<0.001)	0.23
	LAZ	*6 weeks*			
		Birth WAZ	0.61‡	0.49, 0.73 (<0.001)	0.24
		Infected vs. Uninfected mother	-0.37‡	-0.74, -0.01 (0.046)	0.73
		16 weeks			
		Birth WAZ	0.54‡	0.42, 0.67 (<0.001)	0.25
Goga et al 2012 [35]	HIV transmission or death	*vs. No BF, Paarl*			
		Rietvlei			
		No BF	5.60#	1.8, 17.0	9.44
		EBF + <12 week weaning	2.80#	0.6, 13.1	21.80
		MBF	2.70#	1.0, 7.2	7.20
		Paarl			
		EBF + <12 week weaning	1.90#	0.2, 1.5	7.50
		MBF	4.30#	1.2, 16.0	13.33
		Umlazi			
		No BF	4.10#	1.2, 13.7	11.42
		EBF + <12 week weaning	1.90#	0.7, 5.2	7.43
		MBF	2.10#	0.6, 6.7	11.67

*Confidence interval (CI) ratio or difference reflects measurement precision. The CI ratio is the UCL/LCL and is used for all logistic regression models. The CI difference is the UCL – LCL and is used for linear regression models.#Hazard ratio ǂOdds ratio ‡linear regression coefficient ¥rate ratio s.e. standard error

Table 10 Results from meta-analyses

Authors	Outcome	Comparison	Measure of Association	95% CI (p-value)	CI ratio (difference)*
RCTs					
Taha et al 2010 [36]	WAZ	Not BF vs. BF	-1.08‡	-1.16, -0.99 (<0.001)	0.17
	LAZ		-0.62‡	-0.73, -0.52 (<0.001)	0.21
	WLZ		-0.64‡	-0.77, -0.52 (<0.001)	0.25
Newell et al 2004 [37]	Mortality	Ever BF vs. Never BF	0.94‡	0.50, 1.75 (0.84)	3.50
		Maternal death	3.65‡	1.92, 6.96 (0.0001)	3.62
		Maternal CD4 < 200 cells/μl vs. CD4 > 500 cells/μl	1.72‡	0.92, 3.22 (0.09)	3.50
Observational					
Becquet al 2009 [38]	HIV transmission	BF < 6mths vs. BF >6mths	1.80#	0.9. 3.4 (0.06)	3.78
		Solids ≤2months	2.90#	1.1, 8.0 (0.04)	7.27
		Maternal CD4 < 200 cells/μl	2.90#	1.7, 5.1 (<0.001)	3.00

*Confidence interval (CI) ratio or difference reflects measurement precision. The CI ratio is the UCL/LCL and is used for all logistic regression models. The CI difference is the UCL – LCL and is used for linear regression models. #Hazard ratio ǂOdds ratio ‡linear regression coefficient ¥rate ratio s.e. standard error

3.1 Feeding

Feeding definitions

The WHO has defined the different feeding modalities (as outlined in the protocol, table 3). It is against these definitions that feeding across studies will be assessed.

The studies included in this review emphasised that mixed feeding is most commonly practised, whether from birth or shortly thereafter [14, 20–24, 29, 31, 35, 37]. Assessing feeding is inherently difficult and is usually based on self-reports [15–17, 19, 20, 28, 29, 31, 32, 35, 37]. Even in studies where feeding was randomised [14, 21–23], compliance was based on maternal reports. These may be strongly influenced by social desirability bias. The inconsistencies with feeding definitions and the difficulties in ensuring that feeding modality can be defined as per the WHO feeding classifications limits the comparability across studies where feeding and growth, morbidity or mortality were examined.

For example, one study had grouped infants who were mixed fed with formula fed infants and compared this group to exclusively breastfed infants [31]. Other studies had exclusive breastfeeding (EBF) defined for shorter periods compared to the 6 months encouraged by the WHO [15–20] although one was the ZEBS trial where the aim was to assess the impact of shortened duration of EBF to 4 months on MTCT and other infant outcomes. Owing to this complexity, many studies compared infants that had ever been breastfed to infants that had never been breastfed (formula fed), thus losing the ability to examine the impact of duration of breastfeeding, particularly EBF, on growth, morbidity and mortality.

Feeding modality compliance

In addition to the difficulty in defining feeding modality, compliance with a feeding modality whether it was one selected by the mother herself or one to which she was randomised, is frequently low. For example, compliance to randomisation in the Kenyan trial [21] was 70% in the formula feeding arm and 96% in the breastfeeding arm. Compliance in the breastfeeding arm decreased over time – 95%, 90% and 80% compliance at 3, 6 and 12

months respectively. EBF had even lower rates of compliance – 83% at 6 weeks, with a large drop by 3 (62%) and 6 (9%) months [21]. When specifically looking at HEU infants [23], 15% of breastfed and 10% of formula fed infants were receiving solids by 3 months of age (median age of introduction 4.5 months). In the Mashi trial [14], compliance in the formula feeding arm was reasonably high (93%), however, like the Kenyan trial, compliance in the breastfeeding arm decreased over time. In the Mashi trial mothers in the breastfeeding arm were encouraged to practice EBF. Compliance to EBF was 57%, 31.3% and 17.5% at 1, 3 and 5 months respectively. At 3 months nearly 50% of those in the EBF arm were practising mixed feeding (MF) and by 5 months this had increased further to 75%.

In a Tanzanian study, the practice of EBF was also poor, with only 30% of infants exclusively breastfed for longer than 3 months [29]. A South African study found that 28.5% of mothers never breastfed their infants [20], and in a pooled analysis 51% of South African infants had not been breastfed compared to 2% of infants in east and west Africa [37]. A Ugandan study found that, where mothers had been counselled to practice EBF for 3-6 months, 92% of mothers practised EBF for a median duration of 4 months, stopping at a median age of 5 months. By 6 months, 48% had been weaned from BF completely, 25% were still EBF and 20% were MF [28].

In studies conducted in South Africa, the proportion of MF infants ranged from 15.4% MF at 6 months [32] to 48% partially BF and 52% predominantly BF by 12 weeks of age [35] even though breastfeeding initiation was high (95%) in the latter study. Partial and predominant BF are sub-categories of mixed BF as detailed in the WHO feeding definition table (table 3 in the protocol). It is important to note that the study conducted by Coovadia et al [32] was an intervention cohort, with mothers receiving frequent support (antenatal counselling and regular postnatal support) with infant feeding, regardless of which modality was chosen although mothers were encouraged to exclusively breastfeed. In contrast, Goga et al looked at breastfeeding practices at PMTCT sites to determine a baseline of feeding practices and

the results was similar to a study conducted early in the HIV/AIDS pandemic where 57% of infants were MF [31] .

A major benefit of the study conducted by Goga et al is that they found a differential in breastfeeding rates, dependent on the resource capacity of the study site [35]. In this study, an urban site had a greater number of infants initiated on FF (75%) compared to the peri-urban (58%) and rural (21%) sites. Resource capacity also had an impact on HIV transmission, as discussed below.

Introduction of solids

Although never breastfed leads one to think that formula feeding was exclusive, this may not necessarily be the case. Mothers may formula feed, and not breastfeed, their infants but still introduce solids or other non-milk liquids too early. This too comprises mixed feeding as defined by the WHO. Goga et al defined formula feeding in combination with other foods (liquids and solids) as mixed formula feeding and in their study 67% of HIV infected mothers who had never breastfed their infants (47% of HIV infected mothers) were practising mixed formula feeding by 3 weeks of age.

3.2 Growth

Feeding and growth

Growth was assessed by studies, most frequently, by looking at z-scores for weight-for-age (WAZ), length-for-age (LAZ) and weight-for-length (WLZ) [18, 22, 23, 25, 30, 36]. Mbori-Ngacha et al found that after adjusting for HIV infection, infants who were breastfed had a better nutritional status (WLZ) compared to formula fed infants, particularly during the first 6 months of life. During follow-up, 7% of breastfed HEU infants and 11% of formula fed HEU infants were malnourished, and found to have WLZ < -2SD [22]. In the retrospective cohort study conducted by Landes et al, in which all infants received some BM, 4% of HEU had a WAZ <-2SD or LAZ < -2SD [30].

In studies focussing on growth among HEU infants only, not breastfeeding was associated with worse growth (WAZ, LAZ or WLZ) outcomes [15, 23, 26, 33, 36]. In the ZEBS trial analysis specifically focussing on growth among HEU infants a sharp decline in WAZ was observed in all infants between the ages of 4.5 and 15 months. In infants who were not weaned abruptly at 4 months but continued to BF, the decline in WAZ was lessened [18]. As randomised, infants assigned to early cessation had a mean (± standard deviation) WAZ of -0.61 ± 0.07 at 4 months, while the control group, who continued breastfeeding, had a mean WAZ of -0.55 ± 0.07. However compliance with abrupt weaning was low and a per protocol analysis showed that infants who actually stopped breastfeeding abruptly had a mean WAZ of -0.89 ± 0.34 (14.3% <-2 SD WAZ), and infants who continued breastfeeding had a mean WAZ of -0.57 ± 0.05 (9.4% <-2SD WAZ) at 4 months of age. By 6 months of age, infants who stopped breastfeeding (as practised) had a mean WAZ of -0.78 ± 0.08 (13.1% <-2SD WAZ) and infants who continued breastfeeding had a mean WAZ of -0.61 ± 0.06 (10.6% <-2SD WAZ). Thus, it is clear that growth slowed over time, but the effect was somewhat ameliorated by breastfeeding.

Early weaning, defined as the introduction of cow‘s milk at or before 6 weeks of age was also found to negatively affect growth [25]. In the secondary analysis conducted by McGrath et al [23], both an intention to treat (ITT) and per protocol (PP) analyses were conducted due to poor compliance to feeding randomisation as discussed previously. In the ITT and PP analyses the results were fairly consistent and showed that not breastfeeding had a negative impact on growth (particularly WAZ and WLZ), although like in the ZEBS study this effect may be attenuated in the ITT analysis due to poor compliance. Little difference was found in either the ITT or PP analysis when looking at the effect of feeding on stunting; thus, neither formula feeding nor breastfeeding was protective against stunting and other factors may play a greater role in the risk of being stunted. Stunting is indicative of chronic under-nutrition thus maternal education [40], food security, socio-economic factors and intercurrent

infections may be of greater importance. Breastfeeding cessation was also found to have a negative impact on all growth parameters [18].

Birth anthropometry, maternal factors and growth

Infant birth weight has an impact on postnatal growth as well – a higher birth weight (and other birth anthropometric measures) is associated with higher post-natal anthropometric z-score whereas a birth weight <2 500g has a negative effect on postnatal z-scores although growth velocity is frequently faster in this group due to catch-up growth [15, 18, 23, 25, 33]. In the ZEBS trial, one analysis looked at the effect of actual birth weight on growth [15] as opposed to z-scores, with the study examining the effect of each 100g increase in birth weight. In the analysis looking at growth (specifically mean postnatal WAZ by birth weight) in HEU infants in the ZEBS trial, at 1 month of age, low birth weight (LBW) infants had a mean WAZ of -2.19, improving to -1.65 by 6 months of age. Normal weight infants had a mean WAZ of -0.33 at 1 month of age, decreasing to -0.58 by 6 months of age [18]. Although infants with a normal birth weight had a greater WAZ at 6 months of age compared to low birth weight infants ($p < 0.0001$) this was mostly due to a higher weight at birth and 1 month of age, with growth actually being better among LBW infants, compared to normal weight infants. In the Kenyan trial, z-scores were classified as <-2SD for WAZ, LAZ and WLZ and not analysed as a continuous variable over time or separated by LBW and normal birth weight. However, the authors reported a non-significant increase in both WAZ and WLZ during the first 6 months, followed by a decline in weight in both BF and formula fed (FF) infants. No differences in the rate of change in WAZ or WLZ were found by feeding modality in either the PP or ITT analyses [23].

The VTS study found that the change in WAZ by birth weight with age (in weeks) was -0.0037 (95% CI -0.0055; -0.0017 $p < 0.001$) for normal weight infants and 0.02 (95% CI 0.014; 0.027 $p < 0.001$) for LBW infants [33]. Once again the results show faster growth, over time, for LBW infants but slower growth among normal weight infants.

Maternal factors, particularly death 4 months after delivery [15] and advanced (low CD4 count or high viral load) maternal disease [18, 25, 33], were also associated with worse infant growth over time. Lastly, Muhangi et al found that HEU infants were at increased odds of poor growth compared to unexposed infants [25].

In a Zambian study looking at growth and HIV the authors unfortunately did not have ethical approval to test infant HIV status [34]. The authors tried to work around this limitation by only assessing growth information of infants of infected mothers who could be traced, and thus were still alive between the ages of 2-4 years. Once again, birth anthropometry was an important determinant of growth, while in this study population maternal HIV status only seemed to influence LAZ at 6 weeks of age.

3.3 Morbidity and mortality

Feeding modality and mortality

The risk of mortality in breastfed and formula fed infants was not consistent across trials investigating the effect of feeding modality on death. The Kenyan trial found that mortality was similar between BF and FF infants [21]. In a subsequent analysis, Mbori-Ngacha et al [22] found FF to be 28% protective against the combined outcome of death and HIV transmission. The authors also looked at a subset of infants who remained uninfected for the duration of the follow up period. The infants in the BF arm had a cumulative mortality rate of 8.1% compared to the FF arm at 10% (p=0.59).

The pooled analysis of seven studies by Newell et al [37] found that mortality did not differ significantly between ever and never BF infants while Natchu et al found an inverse relationship between EBF and mortality, with EBF associated with lower mortality, between birth and 5 months of age [29]. No information was provided on MF. In the Mashi trial, EBF infants had a lower risk of mortality compared to FF infants through to 7 months of age [14]. The Ugandan study had similar results to the Mashi trial, finding BF to be protective against mortality and infants who were breastfed (EBF and continued BF) for less than 6 months had

a 6-fold increased risk of mortality compared to infants breastfed for more than 6 months [28].

Maternal factors, birth weight and mortality

Maternal death and advanced disease also increased the risk of infant mortality [15, 30, 37]. Kuhn et al found a differential effect between feeding modality and mortality depending on the severity of maternal disease as well as infant birth weight <2 500g [19]. There was an increased hazard of mortality in those who adhered to the intervention i.e. stopped breastfeeding at 4 months of age. The increased hazard associated with weaning was greater in those with a maternal CD4 count >350 cells/μl compared to those with lower CD4 cell counts. The control group (continued BF) also showed an increase in mortality once breastfeeding was stopped. Landes et al also found that HIV exposure and a birth weight <2 500g increased the risk of death among infants [30].

Feeding modality, maternal factors and morbidity

In the Zambian trial, no difference was found between feeding modalities for the incidence rates of diarrhoea or pneumonia when infants were stratified by infection status [22]. McGrath et al [23] found that an episode of diarrhoea within the past month, meant a 2-fold increased risk of wasting (WLZ <-2SD) compared to infants who had not had diarrhoea (similar in both the ITT and PP analyses).

Studies were in agreement that advanced maternal disease increased risk of HIV infection and other morbidities, including hospitalisation [15, 19, 24]. The PEPI-Malawi trial found that for general morbidities, breastfeeding was protective at 6-9, 9-12 and 12-15 months of age [26].

Bobat et al examined morbidity, specifically otitis media, diarrhoea and pneumonia in relation to feeding modality [31]. No incidence of morbidity was seen in FF infants, therefore in order to calculate a risk ratio the authors combined FF and MF infants and compared them to BF infants. This study was conducted during the earlier stages of the HIV pandemic in South

Africa, before the use of ARVs and current knowledge on mixed feeding. Instead of grouping MF and FF infants, the authors should rather have compared morbidity between MF and EBF infants.

Nuanced feeding modality duration and HIV transmission

When looking at morbidities and risk of HIV transmission, cohort studies provided an additional nuance by including feeding type and duration [31, 32, 35, 38]

In a non-randomised intervention cohort conducted in South Africa [32] an increased risk of infection was found for mixed feeding, specifically looking at infants who were HEU at 6 weeks of age. Advanced maternal disease and a birth weight of <2500g were also associated with an increased risk of infection.

In a pooled analysis of a South African and west African study, Becquet et al [38] found an increased risk of transmission among infants breastfed for >6 months, and found that this risk increased by 1% (CI ratio 3.40) for each additional month of BF beyond 6 months. It is important to take into account that in this pooled analysis the PMTCT regimens differed between the two studies – the South African study (study one conducted by Coovadia et al, mentioned above) only provided single dose nevirapine, while the Ditrame Plus study used zidovudine and/or lamivudine together with single dose nevirapine.

Resource availability, HIV transmission and mortality

Goga et al [35] showed that the risk of a combined end point of either HIV infection or death by 9 months of age, by feeding modality, was site dependent. Paarl, a well-resourced site with an infant mortality rate (IMR) of 40/1 000, had a lower risk of either transmission or death if infants were exclusively formula fed. In contrast, the two sites with high IMRs (Rietvlei 99/1 000 and Umlazi 60/1 000) had lower risk of transmission or death if infants were exclusively breastfed and weaned early. When this study was conducted, single dose nevirapine was the basis of PMTCT in South Africa [41].

4. Study comparability

Many studies where HEU infants are included as study subjects focused mainly on either HIV transmission [14–17, 20, 24, 31, 32, 38], death [19, 26, 28–30, 37], or a combined end point [35]. The health outcomes among HEU infants only came to the fore once PMTCT programmes were proven to be successful. This includes the growth of HEU infants.

The Kenyan and Mashi trials were the only studies in which feeding modality was randomised antenatally [14, 21–23]. In all other studies, feeding was either standard for a set time followed by randomisation to continued breastfeeding for as long as the mother decides or abrupt cessation [15–19] or feeding modality was the mother‘s decision, based on informed choice. Furthermore, regardless of feeding modality decided upon, the recorded compliance to assigned method or method of choice was always based on self-report. The lack of an objective measure to assess feeding modality is one of the inherent difficulties in investigating infant feeding.

The results tables contain confidence interval (CI) ratios or differences as these are a better indication of measurement bias than the CI or the p-value [42]. The CI ratios reflect measurement precision, and in studies where these ratios (or differences) were particularly large, it was related to small sample size. For instance, in the Kuhn et al study [15], very few infants ceased breastfeeding before 4 months (36 vs. 584 still breastfeeding at 4 months), had a birth weight of <2 500g (86) and had mothers die within 4 months of delivery (16), thus explaining the size of the CI ratios. Another example is the analysis where McGrath investigated growth in HEU infants - the CI ratios indicate that measurement was fairly precise and that there is an increased risk of being underweight or wasting when breastfeeding is avoided despite a p-value of >0.05. The p-value is an arbitrarily chosen reflection of statistical significance [42, 43].

Lastly, it is worth mentioning that the rates of EBF reported in the intervention cohort study was higher than reported in all studies [32]. As the authors mentioned, this is related to the intensive counselling the mothers received on infant feeding, both antenatally and postnatally. Many studies did not provide intensive support for EBF even if mothers were given the information to make an informed choice on feeding modality. Rates of EBF were generally low in studies where EBF was investigated [20, 35], with a rapid decline over time emphasising the challenges mothers face sustaining EBF for 6 months as advised by the WHO.

4.1 Study concerns

In this review, results from trials that were not originally designed to investigate growth or feeding were included [20, 24, 25]. Thus the results of these studies, although included in the trials table, represent cohort studies as subjects were a sub-group of the entire trial sample. Despite not originally designed to investigate growth or feeding of HEU infants, these studies provided much needed information on HEU infants.

In a study conducted during the early stages of the HIV/AIDS pandemic in South Africa, the authors did not report any details on the introduction of solids [31]. The authors mentioned that infants would have received complementary foods for varying periods but median age of introduction was not assessed. This is important, as early introduction of non-milk feeds constitutes mixed feeding and the authors mentioned the overall median duration of EBF for the whole group was 5 months, with the median duration among mothers practising EBF as 12 months. This contradicts the WHO feeding definitions as EBF is only supposed to occur for the first 6 months when the introduction of solids or complementary foods for the purposes of weaning onto family foods should commence [13, 44].

5 Conclusion

When looking at South Africa, breastfeeding rates, particularly EBF rates, are low. In the study conducted at PMTCT sites, Goga et al also included uninfected mothers and found that mixed feeding was the norm for the uninfected population too. Ninety-five percent of uninfected mothers initiated breastfeeding, and although by 3 weeks 93% were still breastfeeding, this decreased to 73% and 66% by 12 and 36 weeks respectively. EBF rates were even lower; 17% and 3% at 3 and 12 weeks respectively [35].

Breastfeeding is important for infant health, whether infants are HIV-exposed or unexposed, and longer duration of breastfeeding should be supported for all mothers. HIV infection in mothers increases the complexity of generic feeding advice; these mothers require more intensive assistance and advice in order to maintain the health of their infants, and keep them uninfected. Breastfeeding, infant growth and infant morbidity are interlinked as evidenced by the studies included in this review.

With the success of PMTCT programmes, the focus is slowly shifting from merely treating HIV-infected infants, but keeping HEU infants uninfected and optimising their health outcomes, including growth, too. The health needs of HEU infants are not well known, and the long term consequences of both *in utero* and breast milk exposure of ARVs are also not known, but research in the field continues. Key to this, is describing the HEU cohort, and maintaining follow-up for as long as possible, particularly as most studies stop follow-up around 24 months of age.

As the number of infants who are exposed yet uninfected will increase in number, future research should endeavour to understand baseline characteristics of these infants, their impact on future growth and health outcomes, and how they compare not only to exposed infected infants, but unexposed infants too. Few studies included a control group of

unexposed infants, without which the health needs and outcomes of HEU infants in comparison to the general infant population cannot be adequately understood. This includes examining growth outcomes, and whether or not HEU infants fare worse or are on par with unexposed infants for a given population. Furthermore, feeding is an integral component of child health, and novel ways of confirming reported compliance are needed to make it less subjective.

It is important to remember, that most studies looking at feeding did so in a fairly controlled environment. As PMTCT programmes continue to succeed, the coverage and use of ART will increase. Investigating the effects of feeding and maternal ART in a ‗real world' setting is also needed to confirm the effects of feeding modality on growth shown in study populations.

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Part C: Manuscript[1]

[1] This manuscript follows the author instructions for the journal *BMC Pediatrics*. These instructions are detailed in the Appendix E. This manuscripts deviates from the instructions for readability, thus tables and figures are included in text rather than in an appendix. However, supplementary material is in the appendix. The referencing style (used throughout this dissertation) is as required by *BMC Pediatrics.* author instructions for the journal *BMC Pediatrics*.

Growth of HIV-exposed uninfected infants in the first 6 months of life in South Africa: the IeDEA-SA collaboration

Abstract

Background: HIV-exposed uninfected (HEU) infants are a growing population in southern Africa especially with the increasing coverage of more effective prevention of mother-to-child transmission (PMTCT) antiretroviral therapy regimens. This study describes the characteristics of South African HEU infants, investigates factors impacting birth weight and assesses their growth within the first 28 weeks of life.

Methods: This is a retrospective cohort based on routine clinical data provided to the International Epidemiologic Databases to Evaluate AIDS, Southern Africa (IeDEA-SA) collaboration. Linear regression assessed factors affecting birth weight-for-age z-scores (WAZ) while growth (longitudinal WAZ) was assessed using mixed effects models.

Results: The growth of 2621 HEU infants was assessed. The median birth WAZ was -0.65 (IQR -1.46; 0.0) and 51% were male. The feeding modalities practised were as follows: 0.5% exclusive breastfeeding, 7.9% unknown breastfeeding exclusivity, 78.6% mixed breastfeeding and 10.6% formula feeding. Mothers with a CD4 <200 cells/µl delivered infants with a lower birth WAZ (adjusted ß -0.253 [95% CI -0.043; -0.072], p = 0.006) compared to mothers with a CD4 ≥500 cells/µl. Similarly, mothers who did not receive antiretroviral (ARVs) drugs delivered infants with a lower birth WAZ (adjusted ß -0.49 [95% CI -0.78; -0.20], p = 0.001) compared to mothers who received antenatal ARVs. Antenatal maternal ARVs and CD4 cell count did not have an effect on postnatal growth. Exposure to breast milk positively influenced growth, albeit the effect was small. Infants with a birth weight <2 500g (ß 0.069 [95% CI 0.061; 0.078], p <0.0001) experienced faster growth within the first 28 weeks of life compared to infants with a birth weight ≥2 500g.

Conclusion: Less severe maternal disease and the use of ARVs positively impacts birth weight in this cohort of South African HEU infants. Mixed feeding was common and any breastfeeding may have a positive effect on longitudinal growth.

Introduction

HIV-exposed uninfected (HEU) infants are a growing population in sub-Saharan Africa, particularly with increasing coverage of more effective prevention of mother-to-child transmission (PMTCT) regimens such as option B/B+, antiretroviral therapy (ART) for all pregnant and breastfeeding women either until cessation of breastfeeding or lifelong [1]. In 2010, an evaluation of the South African PMTCT programme, where antenatal HIV prevalence was 32%, found the overall early HIV transmission rate (4-8 weeks postpartum) to be 3.5% [2] — indicating a large number of exposed but uninfected infants. More recently, antenatal HIV prevalence is 29.5% in South Africa and both effectiveness and coverage of PMTCT have improved [3].

Breastfeeding is known to transmit HIV, however its importance for infant nutritional status [4–8] and protection against morbidity [9] and mortality [10–13] is also well documented. In South Africa particularly, mixed feeding, defined by the World Health Organization (WHO) as a combination of breast milk and/or infant formula, other liquids and solids [14, 15], is common. In an evaluation of the South African PMTCT programme, 53% of HIV-infected mothers breastfed their infants, of which 42% practised exclusive breastfeeding (EBF) at 3 weeks of age. By 12 weeks of age, however, only 18% of HIV-infected mothers who breastfed their infants were practising EBF. Among HIV-infected mothers who practised mixed breastfeeding (MBF) at 12 weeks of age, 48% and 52% of infants were partially (breast milk and non-nutritive and nutritive solids and liquids) and predominantly (breast milk and non-nutritive liquids) breastfed respectively [14]. Similarly, Coutsoudis et al found 57% of infants were mixed fed in a study conducted early in the HIV/AIDS pandemic, prior to the PMTCT programme [9], thus mixed feeding is widely practised in South Africa.

Longitudinal growth is not only affected by feeding but by birth weight and maternal factors too. Infants with a higher birth weight have greater postnatal weight-for-age (WAZ) over time compared to low birth weight (LBW) infants (<2 500g) although postnatal growth rate in the

first year of life is faster in LBW infants [4, 5, 8, 16, 17]. There have been conflicting findings with respect to the effect of feeding on growth. McGrath et al found no differences in the rate of growth between ever breastfed and formula fed infants, with WAZ increasing during the first 6 months after which they declined [8]. However, Malawian studies found that not breastfeeding was associated with both an increased risk of being underweight (WAZ <-2) as well as having lower weight-, length- and weight-for-length z-scores compared to infants who were breastfed [6, 7]. The Zambia Exclusive Breastfeeding Study found that among all HEU infants there was a decline in WAZ between 4.5 and 15 months, but that in infants who had continued breastfeeding at 4 months, the decline was lessened [16]. The early introduction of cow's milk (≤ 6 weeks of age) was also found to have a negative impact on growth [17]. The effect of feeding modality on growth may in part be context-dependent, and affected by the extent to which the AFASS (affordable, feasible, accessible, safe and sustainable) criteria for replacement feeding are met [14]. Maternal health also impacts child growth: infants of mothers with advanced disease (high viral load, ≥100 000 copies/ml, or low CD4 cell count, ≤350 cells/μl) were found to have slower growth over time [5, 16, 17].

Many previous studies of growth in HEU were conducted outside South Africa, where breastfeeding practices and access to replacement feeding may be different, and prior to widespread availability of effective PMTCT regimens. The aim of this analysis was therefore to assess birth weight and growth within the first 6 months of life in HEU infants from two PMTCT cohorts in South Africa and examine the impact of maternal factors, including disease severity and the use of ARVs, and feeding modality.

Methods

Study design, setting and participants

This was a retrospective cohort study based on routine data provided to the International Epidemiologic Databases to Evaluate AIDS, Southern Africa (IeDEA-SA, www.iedea-sa.org)

collaboration. The IeDEA-SA cohort has been previously described [18, 19], although this is the first analysis of HEU infants. Two South African sites were included in this analysis namely McCord Hospital (MH), KwaZulu-Natal and Rahima Moosa Mother and Child Hospital (RMMCH), Gauteng. MH was a public-not-for-profit programme where a small patient co-payment was required at each visit, while RMMCH is a public hospital where care is provided at no cost to pregnant women and children ≤6 years old. Both facilities provided primary and secondary care. We included infants born from 2007 – 2013. Growth monitoring and promotion was provided based on standard practices at each facility. In South Africa, 2008 guidelines on infant feeding advocated HIV-infected mothers exclusively breastfeed their infants unless replacement feeding met the AFASS criteria, in which case free infant formula was provided for 6 months [20, 21]. The 2010 PMTCT guidelines include ARV regimens. Women were eligible for lifelong ART (tenofovir (TDF) + lamivudine/emtricitabine (FTC) + nevirapine (NVP)) if they had a CD4 ≤350 cells/μl or WHO clinical stage 3/4. Women not eligible for ART (CD4 >350 cells/μl or WHO clinical stage 1/2) received zidovudine (ZDV) from 14 week gestation followed by single dose NVP and ZDV during labour and TDF + FTC after delivery [22]. In 2011, the Tshwane declaration of support for breastfeeding was signed, ending the provision of infant formula for PMTCT in state facilities, like RMMCH [23]. MH continued the provision of infant formulae.

We only included HIV-exposed uninfected infants with at least birth weight and one additional weight measurement within the first 28 weeks of life, with recorded maternal information. We excluded infants diagnosed as HIV-infected (n=126), mostly (97%) before 3 months of age (8.7% diagnosed by 1 month, 89% between 1–3 months, 1.6% between 3–6 months and 0.8% after 12 months of age).

Outcomes

The primary outcome was postnatal growth within the first 28 weeks of life which was assessed using WAZ only. We did not assess growth using length-for-age or weight-for-length as length measurements were not available on all infants at all time points. Factors influencing birth weight were also assessed as birth weight impacts longitudinal postnatal growth.

When assessing postnatal growth, birth weight was considered the baseline and follow-up visits with recorded weights were used to assess growth. WAZ were calculated using the WHO Child growth standards (igrowup, version 3.2.2 2011) package for Stata®. All statistical analyses were done using Stata® (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Variables

We collected data on the following maternal factors: parity (number of previous live births) for the index pregnancy (categorised as 0, 1 and ≥2); maternal age categorised as <18 years (younger), 18-35 years and >35 years (older); antenatal CD4 cell count categorised into <200, 200-500 and ≥500 cells/μl and maternal ARVs grouped into any ARVs (comprising unknown regimen, nevirapine (NVP) only, dual therapy and triple therapy), no ARVs and missing ARV information. Where maternal ARV regimen was changed during the pregnancy, we included the antenatal regimen closest to the delivery date.

Infant variables collected included the following: sex, gestational age (based on palpation or date of last menstrual period) at delivery (categorised as term (≥ 37 weeks), preterm and unknown gestational age), birth weight (categorised as low (<2 500g) or normal (≥2 500g). Infant feeding, as it occurred over 28 weeks, was categorised into formula feeding (FF i.e.

never breastfed), unknown feeding and any breastfeeding (BF). Any BF comprised EBF, BF with unknown exclusivity and MBF.

Analysis

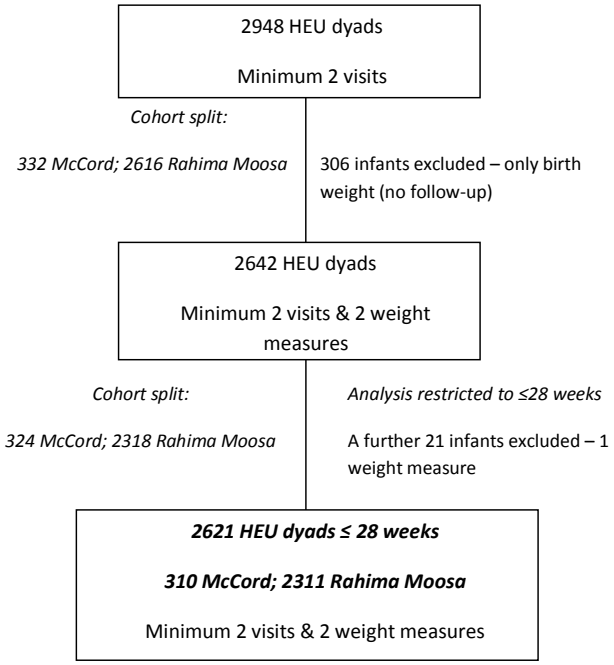
Baseline characteristics between sites were compared using Wilcoxon rank-sum test for continuous variables and Chi-squared or Fisher‘s exact tests for categorical variables.

We first assessed factors affecting birth weight using univariate and multivariate linear regression. We included gestational age, infant sex, maternal age and parity, and cohort in the model *a priori* and then examined the effect of maternal HIV disease (antenatal CD4 cell count and the use of ARVs) adjusted for the *a priori* variables. Univariate and multivariate analyses of the association between demographic, feeding and maternal factors affecting longitudinal postnatal growth were examined using mixed effects models with maximum likelihood estimation. *A priori* inclusions were similar to the linear regression model investigating birth weight outcomes. Feeding modality, infant age (continuous variable, in weeks) and birth weight were additional *a priori* inclusions. The model was then adjusted for maternal and disease-related factors. As growth is time dependent, interaction terms with infant age in weeks were included for all covariates. Covariates (including interaction terms) were included if the p-value was <0.1. As birth weight was a major determinant of postnatal growth, we conducted a sensitivity analysis limited to children with normal birth weight to examine the factors associated with growth in this subset of children. Owing to the nature of routine clinical data, not all variables were assessed at every visit or within the time period of this analysis. Mother-infant pairs were only included in the analyses for birth weight and growth if data on all variables in the models were complete, unless a missing category was included. Cohort was adjusted for in all analyses.

Results

There were 2948 dyads with a minimum of 2 visits, of these 327 (11.1%) were excluded as they did not have at least one visit after birth within the first 28 weeks of life.

Figure 1 HEU profile



Baseline maternal and infant characteristics

The median age at visits within the first 28 weeks was 2.17 months (IQR 1.48; 2.53 months). Majority of the infants in this analysis are from RMMCH (table 1 (a)). Overall, 83% of infants had a normal birth weight (>2 500g) and 51% were male. The overall median birth WAZ was -0.65 (IQR -1.46; 0.00); lower at RMMCH (-0.68, IQR -1.49; -0.04) compared to MH (-0.52, IQR -1.23; 0.31). Gestational age at delivery was only available for 70% of all infants (median 39 weeks, overall; IQR 37; 40). Mixed feeding was most commonly practised overall (78.63%), with large differences between sites; 89% and 0.65% of infants at RMMCH and MH were mixed fed respectively. Most infants seen at MH were formula fed (90%). Maternal characteristics are detailed in table 1 (b). The median maternal age at delivery was similar

between the two sites, with most mothers between 25–35 years old. At MH, where maternal regimen was recorded, 74.8% were on triple therapy (mostly non-nucleo(s)tide reverse transcriptase inhibitors (NNRTI) based), 18.4% on dual therapy, 0.7% NVP only and 3.6% did not receive ARVs. For most mothers at RMMCH who received ARVs for PMTCT, the regimen was not recorded (69.9%). A further 15.5% received NVP only, 0.43% triple therapy, 2.9% dual therapy, and 8.5% did not receive ARVs. For mothers who had antenatal CD4 cell count recorded, 33.6% had a CD4 cell count between 200–500 cells/μl.

Factors affecting birth weight

The models investigating the factors affecting birth weight are found in tables 2 (a) and (b). Infants with a gestational age <37 weeks had a lower birth WAZ compared to term infants (p <0.0001). Females had a lower birth WAZ compared to males (p=0.005), in agreement with previous studies [7, 12, 13, 24–26]. When looking at maternal factors, mothers who received ARVs, irrespective of the regimen, delivered infants with a higher birth WAZ. In comparison to women with a CD4 cell count >500cells/μl, those with lower CD4 cells counts delivered infants with a lower birth WAZ but this was only significant for mothers with a CD4 <200cells/μl (p=0.006). Older mothers (>35 years) gave birth to infants with a significantly lower birth WAZ compared to mothers 25–35 years old (p=0.007).

As a sensitivity analysis these factors (except maternal CD4 and parity where there was substantial missing data) were assessed for the entire HEU cohort, not limited to dyads with complete data on all variables, (table 2 (b)), and they remained consistent, albeit slightly greater in magnitude.

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Table 1 (a) HEU infant characteristics

Characteristics		McCord				Rahima Moosa				Overall			
		n	% missing	median/%	IQR	n	% missing	median/%	IQR	n	median/%	IQR	p-value
	Infants (n)	310				2311				2621			
	% male	53.9%				50.6%				51.0%			0.277#
	normal (>2500g) birth weight (n)	279		90.0%		1892		81.87%		2171	82.8%		
anthropometry	*birth z-scores*												
	birth weight	310	0.0%	-0.52	-1.23; 0.31	2311	0.0%	-0.68	-1.49; -0.04	2621	-0.65	-1.46; 0.00	0.0005*
	males	167		-0.35	-1.09; 0.31	1169		-0.64	-1.42; 0.04	1336	-0.60	-1.42; 0.065	
	females	143		-0.52	-1.47; 0.15	1142		-0.75	-1.56; -0.08	1285	-0.73	-1.52; -0.07	
	birth length	302	2.6%	0.06	-0.62; 1.53	2184	5.5%	0.06	-1.15; 1.12	2486	0.06	-1.00; 1.12	0.0059*
	males	161		0.06	-0.47; 1.12	1109		0.06	-1.00; 1.12	1269	0.06	-1.00; 1.12	
	females	141		0.46	-0.62; 1.53	1076		-0.08	-1.15; 0.99	1217	-0.08	-1.15; 0.99	
	birth head circumference	301	2.9%	0.42	-0.36; 1.21	2178	5.8%	0.10	-0.74; 0.95	2479	0.10	-0.74; 0.95	0.0001*
	males	162		0.42	-0.36; 1.21	1099		-0.36	-1.15; 1.21	1261	0.42	-1.15; 1.21	
	females	139		0.10	-0.74; 0.95	1079		0.10	-0.74; 0.95	1218	0.10	-0.74; 0.95	
delivery	*delivery variables*												
	gestational age (weeks)	156	49.7%	38	38; 39	1674	27.6%	39	37; 41	1830	39	37; 40	0.0411*
	1 min apgar	288	7.1%	8	7;8	1723	25.4%	9	9;9	2011	9	8;9	<0.0001*
	5 min apgar	288	7.1%	9	9;9	1689	26.9%	10	9;10	1977	10	9; 10	<0.0001*
feeding	*Infant feeding (at birth/1st visit)*												<0.0001#
	Exclusive breastfeeding	10		3.2%		3		0.1%		13	0.5%		
	Breastfeeding, exclusivity unknown	1		0.3%		206		8.9%		207	7.9%		
	Mixed feeding	2		0.7%		2059		89.1%		2061	78.6%		
	Formula feeding	279		90.0%		-				279	10.6%		
	Unknown feeding	18		5.8%		43		1.9%		61	2.3%		
visits	visits per patient (n=total obs)	1548		3	2;5	6600		2	1;3	8148	2	1;3	<0.0001*

IQR: inter-quartile range; NVP: nevirapine; AZT: zidovudine; NNRTI: non-nucleot(s)ide reverse transcriptase inhibitors; PI: protease inhibitors *Wilcoxon rank-sum test #Chi-squared/Fisher's exact test

Table 1 (b) HEU maternal characteristics

	Characteristics	McCord			Rahima Moosa			Overall			
		n	median	IQR	n	median	IQR	n	median	IQR	p-value
age	delivery age (years)	310	29.81	25.63; 33.62	2303	29.57	25.54; 33.56	2613	29.61	25.57; 33.56	0.7995*
	age categories										0.473#
	missing	-	-		8	0.4%		8	0.3%		
	younger mothers	63	20.3%		500	21.6%		563	21.5%		
	25-35 years	191	61.6%		1369	59.2%		1560	59.5%		
	older mothers	56	18.1%		434	18.8%		490	18.7%		
parity	*parity*										<0.0001#
	missing	165	53.2%		126	5.4%		291	11.1%		
	0	48	15.5%		481	20.8%		529	20.2%		
	1	62	20.0%		842	36.4%		904	34.5%		
	2+	35	11.3%		862	37.3%		897	34.2%		
CD4 cells/µl	*CD4 cells/µl during pregnancy*	229	316	207; 471	1330	362	240; 501	1559	357	236; 500	0.0140*
	Categorised CD4 cell count										<0.0001#
	missing	81	26.1%		981	42.5%		1062	40.5%		
	<100	10	3.2%		56	2.4%		66	2.5%		
	100-200	38	12.3%		176	7.6%		214	8.2%		
	200-350	81	26.1%		397	17.2%		478	18.2%		
	350-500	47	15.2%		356	15.4%		403	15.4%		
	≥500	53	17.1%		345	14.9%		398	15.2%		
ARVs	*ARV summary*										0.002#§
	no drugs	11	3.6%		196	8.5%		207	7.90%		
	NVP only	2	0.7%		357	15.5%		359	13.7%		
	AZT only or AZT-NVP combination	48	15.5%		66	2.9%		114	4.4%		
	other dual therapy	9	2.9%		-			9	0.3%		
	NNRTI regimen	198	63.9%		10	0.4%		208	7.9%		
	PI regimen	34	11.0%		-			34	1.3%		
	Received ARVs, regimen unknown	4	1.3%		1615	69.9%		1619	61.8%		
	Missing	4	1.3%		67	2.9%		71	2.7%		

IQR: inter-quartile range; ARVs: antiretroviral drugs; NVP: nevirapine; AZT: zidovudine; NNRTI: non-nucleot(s)ide reverse transcriptase inhibitors; PI: protease inhibitors *Wilcoxon rank-sum test #Chi-squared/Fisher's exact test §Any ARVs, no ARVs and missing ARVs were compared

Table 2 (a) Linear regression weight-for-age z-scores including parity and maternal CD4, birth weight; n=1397

	unadjusted			*adjusted*		
variables	**unadjusted ß**	**95% CI**	**p-value**	**adjusted ß**	**95% CI**	**p-value**
Term ≥ 37 weeks	0			0		
Premature[†]	-0.865	-1.03; -0.700	*	-0.829	-0.995; -0.663	*
Unknown GA	-0.056	-0.204; 0.092	0.461	-0.028	-0.176; 0.0120	0.713
Any ARVs	0			0		
No ARVs	-0.490	-0.781; -0.199	0.001	-0.387	-0.668; -0.106	0.007
ARVs missing information	-0.326	-0.876; 0.225	0.246	-0.247	-0.776; 0.281	0.359
25 - 35 years[¶]	0			0		
Young mother	-0.010	-0.165; 0.144	0.895	0.036	-0.123; 0.194	0.657
Older mother	-0.217	-0.378; -0.056	0.008	-0.221	-0.381; -0.061	0.007
Male sex	0			0		
Female sex	-0.200	-0.321; -0.079	0.001	-0.164	-0.280; -0.049	0.005
CD4 ≥500	0.000			0		
CD4 < 200	-0.309	-0.497; -0.122	0.001	-0.253	-0.0434; -0.072	0.006
200 < CD4 < 500	-0.074	-0.217; 0.068	0.305	-0.091	-0.228; 0.045	0.19
parity = 0	0			0		
parity = 1	0.212	0.053; 0.372	0.009	0.263	0.105; 0.420	0.001
parity ≥ 2	0.084	-0.075; 0.243	0.303	0.211	0.042; 0.381	0.015

GA: gestational age †Gestational age <37 weeks ¶Maternal age ‡Not included in model *p<0.0001

Table 2 (b) Linear regression weight-for-age z-scores, birth weight; n=2621

	unadjusted			*adjusted*		
variables	**unadjusted ß**	**95% CI**	**p-value**	**adjusted ß**	**95% CI**	**p-value**
Term ≥ 37 weeks	0			0		
Premature[†]	-0.926	-1.07; -0.784	*	-0.865	-1.007; -0.724	*
Unknown GA	-0.405	-0.515; -0.294	*	-0.398	-0.510; -0.287	*
Any ARVs	0			0		
No ARVs	-0.492	-0.678; -0.306	*	-0.375	-0.556; -0.194	*
ARVs missing information	-0.507	-0.816; -0.198	0.001	-0.376	-0.677; -0.074	0.015
25 - 35 years[¶]	0			0		
Young mother	-0.025	-0.151; 0.102	0.700	-0.008	-0.130; 0.114	0.902
Older mother	-0.299	-0.432; -0.166	*	-0.251	-0.379; -0.122	*
Unknown age[¶]	-0.978	-1.89; -0.065	0.036	-0.592	-1.481; 0.296	0.191
Male sex	0			0		
Female sex	-0.134	-0.234; -0.033	0.009	-0.110	-0.207; -0.013	0.027

GA: gestational age †Gestational age <37 weeks ¶Maternal age ‡Not included in model *p<0.0001

Table 3 Longitudinal linear regression† weight-for-age z-scores 0-28 weeks

	Model including parity; n=2328						*Model including all infants, n=2621*					
	unadjusted			*adjusted*			*unadjusted*			*adjusted*		
Variables	**unadjusted ß**	**95% CI**	**p-value**	**adjusted ß**	**95% CI**	**p-value**	**unadjusted ß**	**95% CI**	**p-value**	**adjusted ß**	**95% CI**	**p-value**
any breastfeeding	0			0			0			0		
formula feeding	0.362	0.156l 0.568	0.001	0.841	0.349; 1.334	0.001	0.310	0.156; 0.465	*	0.453	0.075; 0.831	0.019
formula feeding x age	0.012	0.004; 0.021	0.005	-0.043	-0.069; -0.018	0.001	0.014	0.008; 0.020	*	-0.021	-0.039; -0.003	0.022
unknown feeding	-0.056	-0.382; 0.270	0.736	0.196	-0.082; 0.475	0.167	-0.109	-0.433; 0.214	0.508	0.106	-0.163; 0.375	0.439
unknown feeding x age	-0.002	-0.017; 0.012	0.761	-0.026	-0.044; -0.008	0.004	-0.005	-0.018; 0.009	0.491	-0.025	-0.041; -0.009	0.002
birth weight ≥2500g	0			0			0			0		
birth weight <2500g	-2.432	-2.539; -2.326	*	-2.447	-2.553; -2.341	*	-2.612	-2.712; -2.512	*	-2.620	-2.720; 2.520	*
birth weight <2500g x age	0.068	0.059; 0.076	*	0.069	0.061; 0.078	*	0.067	0.060; 0.074	*	0.068	0.061; 0.075	*
Male sex	0			0			0			0		
Female sex	-0.086	-0.185; 0.013	0.088	0.048	-0.029; 0.125	0.225	-0.102	-0.200; -0.003	0.044	0.059	-0.015; 0.134	0.119
Female sex x age	0.016	0.010; 0.022	*	0.013	0.007; 0.019	*	0.016	0.010; 0.021	*	0.012	0.007; 0.017	*
age (weeks)	0.032	0.029; 0.036	*	0.016	0.009; 0.023	*	0.036	0.034; 0.039	*	0.025	0.012; 0.038	*
parity = 0	0			0			ǂ			ǂ		
parity = 1	0.159	0.029; 0.290	0.017	0.177	0.078; 0.279	0.001	ǂ			ǂ		
parity = 1 x age	-0.002	-0.010; 0.006	0.700	-0.001	-0.009; 0.006	0.709	ǂ			ǂ		
parity = 2	0.056	-0.075; 0.186	0.404	0.174	0.072; 0.276	0.001	ǂ			ǂ		
parity = 2 x age	-0.007	-0.015; 0.001	0.085	-0.008	-0.016; -0.0002	0.045	ǂ			ǂ		

ǂNot included in the model *p<0.0001†Reference categories: Feeding – any breastfeeding, Birth weight - ≥2500g, Sex – males, Cohort – McCord, parity – 0 children

Effects on growth

The main outcome of this analysis is longitudinal growth of HEU infants. The main model is presented in table 3. This model includes parity and thus excludes all dyads missing information on parity (11.10% overall). The second model in the table shows the magnitude of effects among all infants, excluding any variables with missing information. Lastly, in supplementary table 4, the model including maternal HIV-related variables (CD4 and ARVs) is shown. Dyads with missing maternal age (0.31% overall), maternal CD4 cell count (40.52% overall) and parity are excluded. In the reference group of HEU infants, for male infants of nulliparous women with a birth weight >2 500g born at RMMCH and who received breast milk, WAZ increased from birth through to 28 weeks of age (adjusted ß 0.016, p <0.0001).

As expected, infants with a low birth weight (LBW) had a lower birth WAZ compared to normal birth weight infants, but over time, growth was significantly faster among LBW infants (adjusted ß 0.07 per week, p <0.0001). Similarly, infants born to women with parity ≥1 had a higher birth WAZ but experienced a slower increase in WAZ; although the latter effect was small (adjusted ß = -0.008) and only statistically significant for infants of mothers with parity ≥2. In this cohort of HEU infants, females experienced faster growth (adjusted ß 0.013, p <0.0001) compared to male infants.

Although FF infants (and those with missing feeding information) had a greater birth WAZ compared to infants who received any BF (FF infants p = 0.001, missing feeding p=0.167), their growth over time was slower compared to infants who had received any breast milk (FF infants adjusted ß -0.04 p=0.001, missing feeding adjusted ß -0.03 p=0.004).

When looking at the model including all infants, thus not taking parity into account (table 3), the effects were similar.

Sensitivity analyses

This same analysis was conducted among infants with a birth weight ≥2 500g (as a sensitivity analysis) and the direction of these effects remained the same, although the magnitude tended to be smaller (table 5, supplementary material). A model was run including maternal CD4, ARVs and maternal age (supplementary material, table 4 for all infants and table 6 for normal-weight infants). These maternal factors did not have significant effects on growth over time.

Discussion

In this cohort of HEU infants, mothers with more advanced disease, and those not on ARVs, delivered infants with a lower birth weight compared to mothers with less advanced disease, and those who received any ARVs, whether as prophylaxis or triple ART. In contrast, in this cohort of mostly mixed-fed infants, no maternal HIV disease factors were associated with postnatal growth, with postnatal WAZ increasing in all children.

Maternal HIV infection is associated with preterm deliveries, LBW, and small for gestational age (SGA) infants [27]. There is also some evidence that more severe maternal disease (higher viral load and low CD4) increases the odds of preterm and LBW deliveries [28]. Evidence is mixed for the effect of ARVs on birth weight and preterm deliveries, although triple ART, especially the use of protease inhibitor-containing (PI) regimens, either pre-conception or initiated during pregnancy increases the risk of both LBW and preterm deliveries [27, 29].

We found ARV use protective against LBW. In our study, relatively few women would have conceived on ART and very few were on PI-containing regimens. Maternal triple ART would have been restricted to mothers with advanced disease. In addition, all types of ARV

exposure were combined in this analysis so the effects seen are probably due to the partial mitigation of the effects of severe maternal disease by ARVs.

Most HEU infants in the IeDEA-SA collaboration were not exclusively breastfed: the predominant feeding modalities were MBF at RMMCH and FF at MH. FF infants experienced slower growth compared to MBF infants suggesting that any breast milk exposure has a positive impact on growth. However, the effect was very small and it is difficult to draw robust conclusions given the between-cohort differences in predominant feeding modality as well as other factors that may differ between these cohorts e.g. the provision of free formula changed over time and may have been different at the two sites. Furthermore, we did not have detailed data on other factors that are likely to impact growth, such as maternal education [4, 8, 16, 17] and socioeconomic status [4, 16, 17]. Goga et al [14] found differences between sites for the combined end-point of HIV transmission or death, and Ramokolo et al found differences in growth across the same sites [30], thus the effect of different settings and patient characteristics within these settings are an important consideration. It is important to note the reality that most infants were not exclusively breastfed and many were FF. While this may have changed recently with the introduction of option B/B+ in South Africa, strategies to support breastfeeding and optimise growth outcomes in the context of actual infants feeding choices need to be developed and encouraged.

Advanced maternal disease has been shown to negatively impact on growth [4, 16], although in this analysis, maternal CD4 and the use of ARVs did not have a significant impact on growth. This may be because maternal ARV and CD4 data were limited to the antenatal period and may not reflect the maternal disease status after delivery. In addition, the availability of triple therapy for all women with a CD4 cell count <350 cells/μl after 2010 may have mitigated the adverse effects of severe maternal disease seen in studies prior to such ARV availability.

In this analysis, female infants experienced faster growth compared to male infants. Interestingly, previous studies examining growth among HEU infants have not examined the effect of infant sex [5, 8, 16]. However, Kuhn et al found that female infants had lower actual weight compared to male infants between 1 week and 4 months of age [4], while in a Ugandan study female infants had lower odds of experiencing stunting (length-for-age z-score <-2) or being underweight (WAZ <-2) compared to male infants [17].

Strengths and limitations

The major strength of this study is the large number of mother-infant dyads included and the description of feeding practices and growth in infants in a routine care setting. Most previous studies of growth in HEU infants in South Africa have been restricted to research cohorts and randomised controlled trial data, where results may differ compared to infants in routine care. However, the reliance on routinely collected data meant that a number of key variables were missing. For example, although only 5% of birth length and head circumference were missing, these were not regularly measured and recorded at follow-up visits so we were unable to examine length-for-age and weight-for-length z-scores over time. Furthermore, although standard practice was employed for growth monitoring, no quality assurance processes were in place. Information on ARVs given to infants themselves for PMTCT was inadequate thus we were unable to take it into account. Similarly, the introduction of solids was not routinely assessed and could not be included in the multivariate analyses. A previous study evaluating infant feeding practices found that 47% of HIV-infected mothers did not initiate breastfeeding; however, 67% of these mothers who initiated FF were practising mixed formula feeding by 3 weeks of age [14]. Mixed FF also comprises mixed feeding; as the introduction of solids was not assessed the extent of mixed FF in this cohort of HEU infants is unknown. Since rates of EBF are low, the effect of MBF and the introduction of solids should ideally be assessed in a manner reflecting these changes over

time. Feeding modality and maternal disease severity are known to influence risk of infection in infants [4, 10] which would affect growth. However as opportunistic infections were not routinely recorded at sites, this was not investigated.

As only antenatal maternal disease-related factors were included in this analysis, it could account for our finding of an impact on birth WAZ, but not longitudinal WAZ. The impact of postnatal maternal disease severity may have an impact on infant growth outcomes, particularly if infants are breastfed, as it's been shown that mothers who have more advanced disease have poorer infant outcomes [4, 5, 8, 15–17, 31–33], not merely limited to growth

In our cohort of HEU infants birth WAZ was low, but whether this was as a result of HIV-exposure or not is unknown. A comparison between HEU infants and unexposed uninfected infants is needed to investigate this further. Two South African studies have found that HEU infants have similar growth outcomes compared to unexposed infants, with one study only finding differences between the ages of 25-39 weeks [5, 30].

Conclusion

Despite the limitations imposed by routine clinical data, this analysis shows that maternal ARVs and less severe maternal disease have a positive impact on birth weight. We also found that exclusive breastfeeding was rare in this cohort; however, any exposure to breast milk may have a positive effect on postnatal growth. With the introduction of option B/B+ it will be important to examine the impact on infant feeding pattern, infant morbidity and the impact on growth in the growing population of HEU infants. In addition, the effect of the early introduction of solids on growth, particularly if introduced far earlier than 6 months, should be investigated.

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Part D: Appendices

Addendum A: IeDEA-SA data transfer protocol

2013

IeDEA International epidemiologic Databases to Evaluate AIDS

IeDEA Southern Africa

STANDARD PROCEDURE FOR DATA TRANSFER

Version 3.0/May 2013

Contact: *idea-info@ispm.unibe.ch*
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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 tentacles to the data centre. This is not a problem, but it is requested that a separate document be included with a list of the variables in the dataset and brief descriptions/definitions.**
- It is accepted that there will be missing data for some patients, and even entire missing tables from some sites who simply do not have that data in electronic format.
- It is requested that for security purposes, data tables be encrypted and compressed with WinZip 9 or higher using the AES encryption algorithm prior to sending. The encryption password (minimum of 10 characters long, including upper/lower case, numbers and special characters) should be communicated to the relevant data centre contact person by fax or by telephone.
- The use of UCT's Vula site is encouraged; this is an open-source tool allowing for the secure transfers of data from sites to the Data Centre. Vula is open and accessible 24 hours a day, 7 days a week.
- Please ensure that the dataset has been stripped of personal identifying information prior to sending.
- Please include a unique anonymous identifier for each patient (PATIENT) for cross-reference with your own database. It can be the identifier you are using or a special identifier you create for IeDEA Southern Africa. This anonymisation key must be maintained by the site under secure conditions.
- Sites treating children should please send the date at which they changed from using the WHO 3-stage clinical staging system to the 4-stage clinical staging system.
- This version of the DTF for the first time includes tables and fields specifically for the transfer of data on HIV exposed uninfected (HEU) children. For sites that do not collect data on these patients, the DTF is largely unchanged and these new tables and fields can be ignored.
- 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.
- Infants born to mothers with documented HIV-1 infection (HIV exposed uninfected; HEU)

Notes:

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

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

- HIV-exposed uninfected infants (HEU)

    - Where possible, it is intended that data be transferred on HIV-exposed uninfected (HEU) infants followed-up at the facility irrespective of whether or not their mothers' have undergone PMTCT or been on HAART prior to delivery, and irrespective of whether their mothers received PMTCT or HAART at the same facility.

    - The primary patient record for HEU patients will be in the PAT_HEU table. All patients will be entered into the patient table (PAT) and when HEU patients become HIV-infected they will be entered into the PAT_HIV table.

    - HEU infants who subsequently become HIV-infected will have a single unique anonymous identifier and single record in the PAT, PAT_HEU and PAT_HIV tables. In this way, the infants full history from birth can be recorded by linking the LAB, ART, VIS, OI and other tables to the single patient record in the PAT_HEU, PAT_HIV and PAT tables from birth until the time of HIV diagnosis, and from there until start of ART if infant/child starts treatment.

    - Ideally, data from HEU infants and their mothers should be linked as mother-infant pairs using the LINK table. In other words, the mother will have a record in the PAT and PAT_HIV tables and the infant a record in the PAT_HEU table and these will be linkable via the LINK table. Details of the pregnancy will be recorded using the mother's identifier in the PREGNANCY table. The PREGNANCY table will also include the infant's unique identifier. Infant birth details are recorded in a separate table, INFANT table and this includes both the mother and infant's unique identifiers if they were both treated at the same site.

    - HEU infants not identified at birth or soon after, but during admission or hospital consultation for illness may also be included. Unless the mother is a patient at the facility, it is not necessary to include a record for the mother in this case. The mother's history is unlikely to be known but her exposure to ART, details about gestational age and birth history of the child, and the mother's current health should be recorded as far as possible in the

appropriate tables PAT_HEU, ART, PAR_HEALTH and PREGNANCY tables specifically).

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 appropriate.
- For certain date fields a precise date is obligatory e.g. date of first visit at your facility (FRSVIS_DMY) and date of HAART initiation (HAART_DMY). In patients who commenced HAART at another facility, if the precise date of start of HAART cannot be estimated reasonably accurately, the patient should be entered as treatment experienced and the date of first visit at your facility will be regarded as the date of start of HAART.

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).
- HEU infants/children are exposed to HIV in utero and/or perinatally or through breastfeeding but are not known to be infected at their first recorded visit at the facility (usually at birth or soon thereafter).

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.

- A minimum of two tables are required by all sites. Table 1.1 and either Table 1.2 or Table 1.3 or all three are required by all sites. Table 1.1. (PAT) is required for all patients at their first visit. Table 1.2. (PAT_HIV) is required for HIV-infected patients, with a known infection at their first visit. Table 1.3 is required for HIV-exposed infants who are not known to be infected at their first visit. HEU who subsequently become infected will have a record in PAT, PAT_HEU and PAT_HIV tables with the same anonymous patient identifier.
- Tables 2 to 5.1 are required by **all** sites. If sites are collecting information on HEU patients, table 5.2 is also required.
- Table 6 (LINKAGE DATA) is required only for sites that record information on families
    - For mother-child pairs for HEU infants this is required
- Table 7 (PREGNANCY) is required only for sites that record information on pregnancy electronically.
    - Where possible, if a female patient with documented HIV-1 infection is followed up at a facility and becomes pregnant with or without ARV initiation this table should be completed. For HEU infants, it is particularly important to provide as complete data as possible on the mother‘s pregnancy using this table.
    - If the pregnancy outcome is a live birth, table 8 (INFANT) needs to be completed as well.
- Table 8 (INFANT) is used to record the birth information of a child (both HEU and infected). The birth information includes birth anthropometry, agpars and mode of delivery.
- Table 9 (PAR HEALTH) is required only for patients who commence care before their 16thbirthday.
    - Where possible, this should be completed and updated at each visit as appropriate for HEU infants.
- Table 10 (TB) is required only from sites that record detailed information on episodes of tuberculosis electronically.
- Table 11 (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 ~~“m~~eta-data” for the transfer, should be included with all transfers.

1. **1.1 PAT (Patient data)**: A table containing socio-demographic data on 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**.

1.2 PAT_HIV (Patient data for HIV-infected patients): A separate table containing patient characteristics at start of HAART in HAART treated patients. We propose that this table be called **PAT_HIV**.

1.3PAT_HEU (Patient data for HEU infants): A separate patient table containing similar information to the PAT_HIV table will be used for exposed uninfected infants. We propose that this table is called **PAT_HEU.**

1. **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, including HIV diagnostic tests in the case of HEU infants. One line will correspond to one laboratory result. In other words, most patients will have multiple records in this table. We propose that this table is called **LAB**.
2. **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**.
3. **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. For HEU infants, clinical illnesses (e.g. respiratory tract infections, gastro-enteritis) will be recorded using this table and the associated OI codes, although HIV staging will not be relevant. We propose that this table be called **OI**.
4. **5.1 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. Note that a number of fields in this table only need to be completed for HEU infants, denoted by the prefix HEU_ and highlighted in orange. We propose that this table be called **VIS**.

   5.2 VIS_HEU A table containing additional information from all clinical visits particular to HEU patients. One line will correspond to one visit. For HEU patients both table 5.1 and 5.2 need to be completed as far as possible.
5. **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. The data in this table will be used to link HEU infants with their mothers to generate a database of mother-infant pairs. We propose that this table is called **LINK**.
6. **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. For mothers of HEU infants, this table should be filled in as completely as possible to capture data regarding the mothers' pregnancy history if the mother is a patient at your facility. The infant's unique identifier will also be included in this table. We propose that this table be called **PREGNANCY**.

7. **INFANT (Infant birth data)**: A table containing birth information on infants (HEU and HIV-infected). This will include birth anthropometry. This table is specifically needed for HEU infants. The mother's unique identifier will be included in this table. We propose that this table be called **INFANT**.
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 (especially for HEU patients). Alternatively, this table should be filled in at least once, either for the first visit at your facility or the date of start of HAART.
9. **TUBERCULOSIS (Tuberculosis data):** A table with information on all episodes of tuberculosis (TB). This table is only for sites that record detailed information on TB episodes. Sites that do not collect detailed information on TB episodes should enter the TB episodes in the OI table. One line will correspond to one TB episode. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table be called **TB**.
10. **TRIAL (Enrolment in trials):** A table with information on any trial or research study (apart from cohort analysis of routinely collected data) on which a patient is enrolled. This table is only for sites running trials or research studies. One line will correspond to one trial/research study on which the patient is enrolled. In other words, some patients will have more than one record in this table and some may have no records in this table. We propose that this table be called **TRIAL**.
11. **OUTCOME_REVISED: (Death registry linkage data)** A table with information on updated death status following linkage to registry systems.
12. **MET (Meta-data):** A table comprising key characteristics of the data that is transferred.

2 Variables to be included in core tables

2.1 Socio-demographic characteristics and outcomes (PAT & PAT_HIV & PAT_HEU tables)

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 1.1 – Variables to be included in PAT table

Name	Format and definitions	Description
MERGE	Numeric	Number of merge
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
FACILITY	Text	Text field identifying particular clinic within cohort, if more than facility within the cohort
BIRTH_DMY	DATE (dd-mm-yyyy)	Date of birth Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
BIRTH_Y	Numeric (for example 1960) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of birth
BIRTH_M	Numeric (for example 8) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of birth
GENDER	Numeric with codes: 1 = Male 2 = Female 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Sex / gender of patient
FRSVIS_DMY	DATE (dd-mm-yyyy)	Date of first visit at facility (Note: This date must be entered exactly)
ENTRY	Numeric with codes (see List 1)	Mode of entry to your facility
ENTRY_OTHER	Text	Details of other mode of entry not listed in List 1
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.
LAST_CONTACT_DMY	DATE (dd-mm-yyyy)	Date of last contact Note: This date must be entered exactly.
LAST_CONTACT_T	Numeric with codes (See List 4)	Type of last contact
OUTCOME	Numeric with codes (See List 5)	Outcome including death and loss to follow-up
OUTCOME_DMY	DATE (dd-mm-yyyy)	Date of outcome (Leave blank if outcome is Alive [in care] or Alive [not in care])
OUTCOME_Y	Numeric (e.g. 2004) 8888 = Not applicable or exact date of outcome entered above 9995 = Not ascertained 9999 = Unknown despite attempting	Year of outcome Enter 8888 for patients who have not died, or if exact date of outcome entered above.

Name	Format and definitions	Description
	ascertainment	
OUTCOME_M	Numeric (e.g.12) 88 = Not applicable or exact date of outcome entered above 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Enter 8888 for patients who have not died, or if exact date of outcome entered above. 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
DEATH_N1	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	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_C2	Numeric with codes (see List 6)	For each cause of death, please characterise the contribution of the specific cause.
DEATH_N2	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	For each cause of death, please characterise the contribution of the specific cause.
DEATH_C3	Numeric with codes (see List 6)	For each cause of death, please characterise the contribution of the specific cause.
DEATH_N3	Text with following codes: I = Immediate cause U = Underlying cause/condition C = Contributing cause N = Not available	For each cause of death, please characterise the contribution of the specific cause.
DEATH_TXT	Text	
BRSTFD	Numeric with codes 10 = breastfed, exclusive 11 = breastfed, exclusivity unknown 12 = mixed fed (breastfed & formula fed) 20 = Formula fed (never breastfed) 30 = HEU, feeding information entered in visits table 88 = Not applicable 95 = Not ascertained 99 = Unknown, despite attempting ascertainment	Infant feeding history (0-6 months of age) for infants older than 6 months at first visit. For HEU infants, please enter feeding information into the visits table (table 5.2) (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)	Estimated duration of breastfeeding in months in children who are

Name	Format and definitions	Description
		exclusively breastfed or mixed fed.

Table 1.2 – Variables to be included in PAT_HIV table

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

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

Name	Format and definitions	Description
	99 = Unknown despite attempting ascertainment	
WKS_TB_FHV	Numeric (for example 8)	Duration in weeks since start of TB treatment when HAART was commenced in patients with 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)
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)

Table 1.3 – Variables to be included in PAT_HEU table

Name	Format and definitions	Description
PATIENT	Free (numerical or alphanumerical)	Patient identifier from PAT table
CAREG	Numeric with codes (see List 7)	Primary caregiver at first visit (paediatric patients only – enter 88 for adult patients)
PREG_HIV	0 = Negative 1 = Positive (time unknown) 1.1 = Positive prior to this pregnancy 1.2 = Positive during pregnancy (but before delivery) 1.3 Positive at delivery 1.4 Positive after delivery 95 = Not ascertained 99 = Unknown despite attempting ascertainment	HIV status of infant's mother during pregnancy This information is required especially for HEU infants whose mothers do not have their own PAT record in the patient table with pregnancy information recorded in the PREG table

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

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

List 2 - Codes for mode of infection (MODE)

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

Table name: LU_mode

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

List 3 - Disease codes for FHV_SDI (PAT table) and OI_ID (OI table)

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

Table name: LU:DIS

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

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

	single episode (excluding pneumonia)						
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	Cryptococcosisextrapulmonary	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
Codes	**Description**	**WHO stage (Adult)**	**WHO stage (Paed)**	**Event (Adult)**	**Event (Paed)**	**SDI (Adult)**	**SDI (Paed)**
HERPV*	Visceral herpes simplex infection	4	4	1	1	1	1
HG	Hodgkins Lymphoma	88	88	1	1	0	0
HIST	Histoplasmosisextrapulm.	4	4	1	1	1	1
HPVE*	Extensive human papilloma virus infection	88	2	1	1	0	1
HSM*	Hepatosplenomegaly	88	2	0	0	0	1
HZ*	Herpes zoster (not specified)	88	88	1	1	1	1
HZM*	Herpes zoster (more than one dermatome)	88	88	1	1	0	0

HZS*	Herpes zoster (single dermatome)	2	2	1	1	1	1
ISDI	Isosporiasis diarrhoea (duration > 1 month)	4	4	0	0	1	1
ISDS*	Isosporiasis diarrhoea	88	88	1	1	0	0
KS	Kaposi Sarcoma	4	4	1	1	1	1
LEIS	Leishmaniasis visceral	4	88	1	1	1	0
LEU	Progressive multifocal leucoencephalopathy	4	4	1	1	1	1
LGE*	Lineal gingival erythema	88	2	1	1	0	1
LIP*	Lymphoid interstitial pneumonitis	88	3	0	1	0	1
MC	Mycobacterium avium complex (MAC) or Kanasiiextrapulm.	4	4	1	1	1	1
MCDI	Microsporidosis diarrhoea (duration > 1 month)	4	4	0	0	1	1
MCDS*	Microsporidosis diarrhoea	88	88	1	1	0	0
MCI*	Mycobacterium Immune reconstitution syndrome	88	88	1	1	0	0
MCP	Mycobacterium tuberculosis pulmonary	3	3	1	1	1	1
MCPO	Mycobacterium pulmonary other (excluding BCG in children)	88	88	1	1	0	0
MCX	Mycobacterium tuberculosis extrapulmonary	4	4	1	1	1	1
MCXO	Mycobacterium extrapulm. other (excluding BCG in children)	4	4	1	1	1	1
MNUM*	Moderate unexplained malnutrition (60-80% EWFA)	88	3	0	1	0	1
MNUS*	Unexplained severe wasting or malnutrition (<60% EWFA)	88	4	0	1	0	1
MOLC*	Extensive molluscumcontagiosum	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
Codes	**Description**	**WHO**	**WHO**	**Event**	**Event**	**SDI**	**SDI**

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

90	Other
95	Not ascertained

List 6 - Codes for cause of death (DEATH_C1 – 3)

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

Table name: LU: PAT: DEATH_C

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

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

List 7 - Codes for primary caregiver (CAREG)

Code source: IeDEA SA codes

Table name: LU :PAT :CAREG

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

List 8 - Codes for person informed of the HIV status of the child (DISCL_CG)

Code source: IeDEA SA codes

Table name: LU: PAT: DISCL_CG

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

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 empty 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 empty 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 and definitions	Description
MERGE	Numeric	Number of merge
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
LAB_DMY	Date (for example dd/mm/yy)	Date when specimen was taken
LAB_ID	Text (see List 9)	Code representing the measurement
LAB_V	Numeric (for example 44)	Numeric value of measurement Leave blank if result entered as code (LAB_T)

Name	Format and definitions	Description
UNIT_TXT	Text	?UCT
LAB_VSRES	Numeric with codes: 0 = Negative 1 = Posive 88 = Not applicable 99 = Unknown	results for viro-/serological tests
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	Lower limit of detection of RNA assay
TB_DRUG	Text with codes: INH_L = Isoniazid low dose INH_H = Isoniazid high dose INH_U = Isoniazid – dose unspecified PZA = Pyrazinamide RIF = Rifampicin ETN = Ethionamide ETB = Ethambutol STREP = Streptomycin QUI = Quinolone 88 = Not applicable	TB Drug against which sensitivity has been tested. (Enter 88 for laboratory tests other than viral load)
DRUG_RES	Numeric with codes: 0 = No (Sensitive) 1 = Yes (Resistant) 88 = Not applicable	Is Mycobacterium TB cultured RESISTANT to drug in TB-DRUG field? (Enter 88 for laboratory tests other than viral load)

List 9: Codes for measurement type (LAB_ID)

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

Table name: LU :LAB :LAB_ID

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

TBC*	TB culture
TBM*	TB microscopy
TBS*	TB sensitivity
TG	Triglycerides (mmol/L)
URE	Urea (mmol/L)
WBC	White cell count (x1000/ mm^3)
PCR*	HIV PCR
P24*	P24 antigen
SER*	HIV serology (ELISA)
RAP*	HIV rapid test
HIV_UNK*	Unknown HIV test type but result available

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 and definitions	Description
MERGE	Numeric	Number of merge
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
ART_ID	ATC (for example NVP – see List 10)	Type of antiretroviral drug
ART_TXT	Text	?UCT
ART_SD_DMY	Date(dd-mm-yyyy)	Date of starting each antiretroviral drug (start date). Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
ART_SD_Y	Numeric (e.g. 2003) 8888 = Exact start date entered in appropriate field 9999 = Unknown despite attempting ascertainment 9995 = Not ascertained	Year of starting drug
ART_SD_M	Numeric (e.g. 7) 88 = Exact start date entered in appropriate field 99 = Unknown despite attempting	Month of starting drug

Name	Format and definitions	Description
	ascertainment 95 = Not ascertained	
ART_RS	Numeric with codes (See List 11)	Reason for receiving ART
ART_FORM	Numeric with codes: 1 = Tablet/capsule 2 = Syrup/Suspension 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Type of formulation
ART_COMB	Numeric with codes: 1 = Individual drug 2 = Part of a fixed dose combination 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Is drug part of a fixed dose combination?
ART_ED_DMY	Date(dd-mm-yyyy)	Date of stopping each antiretroviral drug (end date) Enter exact date in this field if known. If unknown leave blank and enter EITHER month and year as far as possible in fields below OR number of doses OR duration in weeks in the appropriate fields.
Name	Format and definitons	Description
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)	Number of doses of drug e.g. 1 for single dose Nevirapine
NO_WEEKS	Numeric (e.g. 12)	Number of weeks of receiving drug e.g. 12 for AZT from 28 weeks of pregnancy delivering at term
ART_END_RS_TXT	Text	?UCT
ART_END_RS	Numeric with codes (See List 12)	Reason for stopping antiretroviral drug
ART_END_RS_REVISED	Numeric	Reason for stopping antiretroviral drug – revised code
INFO_SOURCE	Numeric with codes 1 = Clinical records at this facility 2 = Clinical records/letter from another facility 3 = Patient/caregiver report 4 = Likely protocol in use 90 = Other 99 = Unknown	Source of information about ART

Name	Format and definitions	Description
COMMENTS	Text	?UCT

List 10: Anti-retroviral drugs : (ART_ID)

Code source: ATC classification: Anatomical Therapeutic Chemical
Table name: LU :ART :ART_ID

ATC codes	Antiretroviral treatment
J05A	Drug unspecified (i.e. single drug, totally unknown)
J05A-BEV	Beviramat
J05AE	PI unspecified
J05AE01	Saquinavir (gel, not specified)
J05AE01-SQH	Saquinavir hard gel (INVIRASE)
J05AE01-SQS	Saquinavir soft gel (FORTOVASE)
J05AE02	Indinavir (CRIXIVAN)
J05AE03	Ritonavir (NORVIR)
J05AE03-H	Ritonavir high dose (NORVIR)
ATC codes	**Antiretroviral treatment**
J05AE03-L	Ritonavir low dose (NORVIR)
J05AE04	Nelfinavir(VIRACEPT)
J05AE05	Amprenavir (141W94) (AGENERASE)
J05AE06	Lopinavir/Ritonavir (ABT-378/r, Kaletra)
J05AE07	Fosamprenavir
J05AE08	Atazanavir (Reyataz)
J05AE09	Tipranavir (Aptivus)
J05AE10	Darunavir
J05AE-GW4	GW433908/VX-275 (Drug phase III) (PROGENERASE)
J05AE-MOZ	Mozenavir (DMP-450)
J05AE-TMC	TMC 114 (Tibotec)
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
J05AF11	Telbivudine
J05AF30-COV	FDC5 (Stavudine/Lamivudine, d4T/3TC)
J05AF-ALO	Alovudine
J05AF-AMD	Amdoxovir (DADP)
J05AF-FOZ	Fozivudinetidoxi
J05AF-LDN	Lodenosine (trialdrug)
J05AF-RVT	Reverset
J05AG	NNRTI unspecified
J05AG01	Nevirapine (VIRAMUNE)
J05AG01-SD	Nevirapine (VIRAMUNE) single dose

J05AG02	Delavirdine (U-90152) (RESCRIPTOR)
J05AG03	Efavirenz (DMP-266) (STOCRIN, SUSTIVA)
J05AG-CPV	Capravirine
J05AG-DPC083	DPC 083
J05AG-DPC961	DPC 961
J05AG-EMV	Emivirine (MKC442)
J05AG-ETV	Etravirine
J05AG-LOV	Loviride
J05AG-RPV	Rilpivirine
J05AG-TMC	TMC 125 (Tibotec)
J05A-PBT	Participant in Blinded Trial
J05AR	ART regimen and drug unspecified (i.e. both number and names of drugs totally unknown)
J05AR01	Combivir (Zidovudine/Lamivudine, AZT/3TC)
J05AR02	Kivexa (Lamivudine/Abacavir)
ATC codes	**Antiretroviral treatment**
J05AR03	Truvada (Tenofovir/Emtricabine, TDF/FTC)
J05AR04	Trizivir (Zidovudine/Lamivudine/Abacavir)
J05AR05	Douvir-N (Zidovudine/Lamivudine/Nevirapine)
J05AR06	Atripla (Emtricitabine/Tenofovir/Efavirenz)
J05A-TRM	FDC1 (Stavudine/ Lamivudine/ Nevirapine, d4T/3TC/NVP)
J05AX07	Enfurvirtide (FUZEON, T-20/Ro 29-9800)
J05AX08	Raltegravir
J05AX09	Maraviroc
J05AX-EVG	Elvitegravir (Gilead)
J05AX-VIC	Vicriviroc
L01XX05	Hydroxyurea/Hydroxycarbamid (LITALIR)

List 11: Codes for reason for receiving ART (ART_RS)

Code source: IeDEA SA codes

Table name: LU: ART: ART_RS

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

List 12: Reason for treatment discontinuation (ART_END_RS)

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

Table name: LU :ART :ART_END_RS

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

For example, if a drug was stopped because of treatment failure determined by a declining CD4 count, the stop reason should be coded as 1.3; however if the reason for stopping is simply ~~-t~~reatment failure" with the means of determining this not specified, the stop reason should be coded as 1.

CODE old & HICDEP	REVISEDC	ART_END_RS	AE	CI	FL	OTHER
1	1	Treatment failure (i.e. virological, immunological, and /or clinical failure)			1	
1.1	1.10	Virological failure			1	
1.2	1.20	Partial virological failure			1	
1.3	1.30	Immunological failure – CD4 drop			1	
1.4	1.40	Clinical progression			1	
2	2	Abnormal fat redistribution	1			
3	3	Concern of cardiovascular disease	1			
3.1	3.10	Dyslipidaemia	1			
3.2	3.20	Cardiovascular disease	1			
4	4	Hypersensitivity reaction	1			
5	5	Toxicity, predominantly from abdomen/G-I tract	1			
5.1	5.10	Toxicity – GI tract	1			
5.2	5.20	Toxicity – Liver	1			
5.3	5.30	Toxicity – Pancreas	1			
6	6	Toxicity, predominantly from nervous system	1			
6.1	6.10	Toxicity - peripheral neuropathy	1			
98	6.20	Toxicity - neuropsychiatric	1			
98	6.30	Toxicity - headache	1			
7	7	Toxicity, predominantly from kidneys	1			
8	8	Toxicity, predominantly from endocrine system	1			
8.1	8.10	Diabetes	1			
9	9	Haematological toxicity (anemia …etc.)	1			
10	10	Hyperlactataemie/lactic acidosis	1			
91	11.90	Toxicity, not mentioned above	1			
98	11.99	Toxicity - unspecified	1			
90.1	12	Comorbidity		1		
92.3	13	Drug interaction		1		
92.4	13.10	Drug interaction - commencing TB treatment		1		
92.5	13.20	Drug interaction ended - stopping TB treatment				1
96	14	Pregnancy		1		
98	14.10	Pregnancy intended		1		
96.2	14.20	Pregnancy ended				1
98	15	Social contra-indication		1		
98	16.90	Contra-indication - other		1		
98	16.99	Contra-indication unspecified		1		
96.1	17	MTCT regimen completed				1

CODE old & HICDEP	REVISEDC	ART_END_RS	AE	CI	FL	OTHER
94.1	18.10	Non-compliance				1
98	18.20	Defaulter				1
98	19	Change in treatment not due to side-effects, failure, poor adherence or contra-indication				1
92	19.10	Availability of more effective treatment (not specifically failure or side effect related)				1
92.1	19.20	Simplified treatment available				1
92.2	19.21	Treatment too complex				1
98	19.30	Change in eligibility criteria (e.g. child old enough for tablets; refrigerator no longer available)				1
98	19.40	Protocol change				1
97	19.51	Study treatment				1
98	19.52	Study treatment completed				1
98	19.60	Drug not available				1
93	19.70	Structured Treatment Interruption (STI)				1
93.1	19.71	Structured Treatment Interruption (STI) – at high CD4				1
94	19.80	Patient's wish/ decision, not specified above				1
95	19.90	Physician‘s decision, not specified above (note overlap with standard code				1
95.1	20	Contra-indication expired				1
88	88	Death (note overlap with N/A in other lists)				1
90	90	Side effects – any of the above but unspecified	1			
99.5	95	Not ascertained				1
98	98	Other causes, not specified above				1
99	99	Unknown despite attempting ascertainment				1

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

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 and definitions	Description
MERGE	Numeric	Number of merge
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
OI_ID	Text (for example PCP - see List 3 – Disease codes – under PAT table)	Type of opportunistic event
OI_SD_DMY	Date(dd-mm-yyyy)	Date of start of each opportunistic event. Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
OI_SD_Y	Numeric (e.g. 2001) 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of start of event
OI_SD_M	Numeric (e.g. 11) 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of start of event
OI_ED_DMY	Date(dd-mm-yyyy)	Date of end of each opportunistic event. Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below If OI is ongoing (has not yet ended) leave blank and enter appropriate code in field below
OI_ED_Y	Numeric (e.g. 2001) 8885 = Ongoing 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of end of event
OI_ED_M	Numeric (e.g. 11) 85 = Ongoing 88 = Not applicable (Exact date entered in field above) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Month of end of event
DIAG_METH	Numeric (see List 13)	Method of diagnosis

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

Table name: LU :OI :DIAG_METH

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

2. 5 Follow-up clinic visits (VIS&VIS_HEUtables)

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

Table 5.1 – Variables to be included in VIS table

Name	Format and definitions	Description
MERGE	Numeric	Number of merge
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
VISIT_DMY	Date (for example dd/mm/yy)	Date of visit patient
VISIT_FAC	Numeric with codes 1 = Visit at this cohort's facility 2 = Visit at another facility 99 = Site of visit unknown	Facility at which visit took place
WEIGHT	Numeric (e.g 3.20)	Weight in kilos (kg)
HEIGHT	Numeric (e.g 75)	Height in centimeters (cm)
CTX	Numeric with codes : 1 = yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Cotrimoxazole status
INH_STATUS_Y	Numeric with codes : 1 = Yes 0 = No 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Isoniazid status
FLU_STATUS_Y	Numeric with codes : 1 = Yes 0 = No	Fluconazole status

Name	Format and definitions	Description
	95 = Not ascertained 99 = Unknown despite attempting ascertainment	
HEADC	Numeric (for example 75)	Head circumference in centimeters (cm)
SCHOOL_Y	Numeric with codes 0 = No school 1 = At school 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Schooling for children >5 years. For adults and children less than 5 years, enter 88.

Table 5.2 – Variables to be included in VIS_HEU table

Name	Format and definitions	Description
PATIENT	Free (numerical or alphanumerical)	Patient identifier from VIS table
VISIT_DMY	Date (for example dd/mm/yy)	Date of visit patient from VIS table
CAREG	Numeric with codes (see List 7)	Primary caregiver at start of HAART (HAART_DMY) (paediatric patients only – enter 88 for adult patients)
BRSTFD	Numeric with codes 10 = breastfeeding, exclusive 11 = breastfeeding, exclusivity unknown 12 = mixed feeding (breast- and formula feeding) 13 = Breastfeeding, weaning started (solids introduced) 20 = Formula feeding 21 = Formula feeding, weaning started 88 = Not applicable 95 = Not ascertained 99 = Unknown, despite attempting ascertainment	Infant feeding option at current visit This will be applicable from birth until infant on family foods (paediatric patients only - enter 88 for adult patients)
BRSTFD_PROBLEM	Numeric with codes: Any problems with breastfeeding? Masititis/cracked nipples etc 0 = no problems with breastfeeding 1 = problem with breastfeeding but cause unknown 11 = mastitis 12 = cracked nipples 13 = perceived insufficient milk supply 88 = Not applicable 95 = Not ascertained 99 = Unknown, despite attempting ascertainment	Problems preventing adequate breastfeeding at current visit (HEU patients only – enter 88 for adult patients and known HIV-infected children)
SOLIDS_Y	Numeric with codes 0 = no, solids not introduced 1 = yes, solids introduced 88 = Not applicable	Has the infant been introduced to solid foods yet at current visit (any type e.g. porridge/cereal/vegetables/fruit/yoghurt) (HEU patients only – enter 88 for adult patients

Name	Format and definitions	Description
	95 = Not ascertained 99 = Unknown, despite attempting ascertainment ?type of solids (this assessed in Karl's data from visit 3)	and known HIV-infected children)
MUAC	Numeric	Mid-upper arm circumference in centimeters (cm) (HEU patients only – enter 88 for adult patients and known HIV-infected children)

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 and definitions	Description
MERGE	Numeric	Number of merge
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
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)	Unique patient identifier of family member

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 (PREG table)

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

Table 7 – Variables to be included in PREGNANCY table

Name	Format and definitions	Description
MERGE	Numeric	Number of merge
PATIENT_MOTHER	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
PATIENT_CHILD	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
PREG_DIAG_DMY	Date (dd-mm-yyyy)	Exact date when patient first presents as pregnant
PREG_DUR_DIAG	Numeric (e.g. 12)	Estimated duration of pregnancy in weeks when patient first presents as pregnant
PREG_END_DMY	Date (dd-mm-yyyy)	Exact date of delivery, spontaneous abortion or termination Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
PREG_END_Y	Numeric (e.g. 2003) 8888 = Not applicable (Exact date entered in field above) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of delivery, spontaneous abortion or termination

Name	Format and definitions	Description
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)	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 If the pregnancy outcome is a live birth (1), please complete the infant table as well.
PARITY	Numeric	Number of children
GRAVIDA	Numeric	Number of pregnancies
MIS_PREV	Numeric with codes 0= No 1= Yes	Whether there has been a previous miscarriage
PREM_PREM	Numeric with codes 0=No 1= Yes	Has a previous pregnancy ended in a preterm delivery (prior 37 weeks)
PLANNED_PREG	Numeric with codes 0= No 1 = Yes	Was this current pregnancy planned or not.

3.3 Infant birth information (INFANT table)

Table 8 details information to be included in the INFANT table. This table contains information, at birth, on all children bornfrom a mothers known to be HIV-infected.

Table 8 – Variables to be included in INFANT table

Name	Format and definitions	Description
MERGE	Numeric	Number of merge
PATIENT_MOTHER	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
PATIENT_CHILD	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
BIRTH_DMY	DATE (dd-mm-yyyy)	Date of birth Enter exact date in this field if known. If unknown leave blank and enter month and year as far as possible in fields below.
BIRTH_Y	Numeric (for example 1960) 9995 = Not ascertained 9999 = Unknown despite attempting ascertainment	Year of birth
BIRTH_M	Numeric (for example 8) 95 = Not ascertained	Month of birth

Name	Format and definitions	Description
	99 = Unknown despite attempting ascertainment	
COHORT	Text	Text field identifying the cohort
WEIGHT	Numeric (for example 75)	Birth weight in kilos (kg)
HEIGHT	Numeric (for example 75)	Birth height (length) in centimeters (cm)
HEADC	Numeric (for example 75)	Birth head circumference in centimeters (cm)
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
DELIV_M	Numeric with codes 10 = Vaginal, spontaneous 11 = Vaginal, forceps 12 = Vaginal, vacuum 20 = Caesarean section – primary/elective (before onset of labour and rupture of membranes) 21 = Caesarean section – emergency 22 = Caesarean section – type unknown 88 = Not applicable 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Mode of delivery (paediatric patients only - enter 88 for adult patients)
APGAR1	Numeric (out of 10)	Apgar at birth (out of 10) at 1min
APGAR5	Numeric (out of 10)	Apgar at birth (out 10) at 5min

3.4 Parental Health (PAR_HEALTH table)

Table 9 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 9: Variables to be included in the PAR_HEALTH table

Name	Format and definitions	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	Father‘s treatment if available

Name	Format and definitions	Description
	88 = Not applicable (father HIV negative or deceased) 95 = Not ascertained 99 = Unknown despite attempting ascertainment	

3.5 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 10 – Variables to be included in the table TB

Name	Format and definitions	Description
MERGE	Numeric	Number of merge
PATIENT	Free (numerical or alphanumerical)	Unique, anonymous, patient identifier
COHORT	Text	Text field identifying the cohort
REG_DMY	Date (dd/mm/yy)	Date registered with TB
REGID	Text (eg. 2272007)	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

Name	Format and definitions	Description
		resistance status during the episode.
TB_START_DMY	Date (dd/mm/yy)	Date starting TB treatment
TB_END_DMY	Date (dd/mm/yy)	Date ending TB treatment or date of outcome
CAT	Numeric with codes 1 – Newly diagnosed for the first time 2 – After relapse 3 – After default 4 – After failure 95 = Not ascertained 99 = Unknown despite attempting ascertainment	TB Category
CLASS	Numeric with codes 1 - Pulmonary 2 – Extra-pulmonary 3 – Both pulmonary and extra-pulmonary 4 - Primary 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Classification of episode
SITE	Numeric with codes 1 – Bones/Joints (A18.0) 2 – Lymph nodes (A16.3) 3 – Meningitis (A17.0) 4 – Miliary (A19.9) 5 – Pleura (A16.5) 9 – Other sites (A18.8) 88 – Not applicable as pulmonary or primary only 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Site of disease if extra-pulmonary component diagnosed
REGIMEN	Numeric with codes 1 – 2HRZE 4HR - Regimen 1 2 –2HRZES 1HRZE 5HRE - Regimen 2 3 – 2HRZ 4HR - Regimen 3 4 –Other Regimen 95 = Not ascertained 99 = Unknown despite attempting ascertainment	TB treatment regimen
REG_OTHER	Text	Text field for other regimen not included in codes for REGIMEN field above
TB_OUTCOME	Numeric with codes 1 – Completed 2 – Cured 3 – Failed 4 – Interrupted 5 – Defaulted 6 – Treatment ongoing 7 - Died 95 = Not ascertained 99 = Unknown despite attempting ascertainment	Outcome of TB episode

3.6 Trial/research study enrolment information (TRIAL table)

Table 11 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 and definitions	Description
PATIENT	Free (numerical or alphanumerical)	Unique patient identifier
TRIAL_START_DMY	Date (for example dd/mm/yy)	Date of enrolment onto trial
TRIAL_END_DMY	Date (for example dd/mm/yy)	Date of completion/ disenrolment Leave blank if patient is still enrolled on trial
TRIAL_ID	Free (numeric or text) codes (See List 16)	Name of trial on which patient is enrolled Each site to send their own List with coding and description of trial

List 16: Example of codes for trial name (TRIAL_ID)

Code source: Site to supply own codes

Table name: LU :TRIAL :TRIAL_ID

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

4 Revised Death (Outcome) data

This table contains information about death linkage data.

Table 12 – Variables to be included in the table OUTCOME_REV

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

SOURCE	Text	Source of information update i.e. death registry

5 Meta-data

This table contains information about the data transfer itself.

Table 13 – Variables to be included in the table META

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

6 Facility-data

This table contains information about the data facilities.

Table 14 – Variables to be included in the table FACILITY_SET

Name	Format and definitions	Description
COHORT	Text	Text field identifying the cohort
FACILITY	Text	Text field identifying particular clinic within cohort, if more than facility within the cohort
PATIENT_PREFIX	Free (numerical or alphanumerical)	Prefix of the patient identifier. It includes the name of the cohort and facility and makes the patient identifier unique for the hole IeDEA-database
COHORT_old	Text	Text field identifying the cohort
FACILITY_old	Text	Text field identifying particular clinic within cohort, if more than facility within the cohort
PATIENT_PREFIX_old	Free (numerical or alphanumerical)	Prefix of the patient identifier. It includes the name of the cohort and facility and makes the patient identifier unique for the hole IeDEA-database
PATIENT_PREFIX_orig	Free (numerical or alphanumerical)	Prefix of the patient identifier. It includes the name of the cohort and facility and makes the patient

		identifier unique for the hole IeDEA-database
ECONOMY	Numeric with codes 1 = Urban 2 = Rural	Population served
LEVEL_OF_CARE	Numeric with codes (See List 17)	Level of care
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

List 17: Example of codes for level of care (LEVEL_OF_CARE)

Code source: IeDEA SA codes

Table name: LU :FACILITY_SET: LEVEL_OF_CARE

Codes	Level of care
1	District clinic
2	District hospital
3	Health centre
4	Hospice
5	Ngo clinic
6	Provincial
7	Regional

Appendix B: OASIS ethics approval

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E53-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: [illegible]

12 April 2006

REC REF: 084/2006

Dr. A Boulle
Public Health and Family Medicine

Dear Dr. Boulle

THE OBSERVATIONAL ANTIRETROVIRAL STUDIES IN SOUTHERN AFRICA (OASIS) COLLABORATION

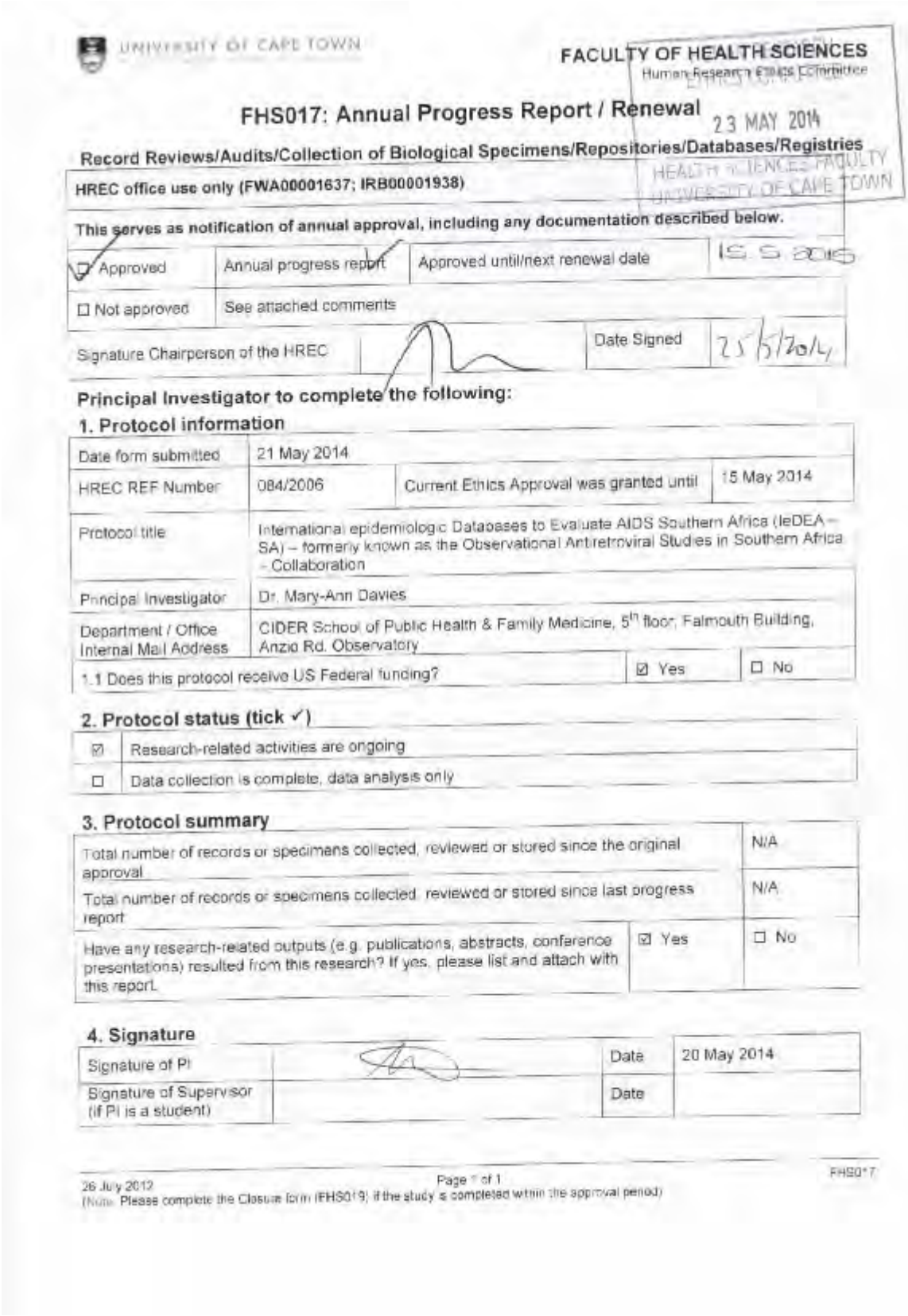
Thank you for submitting your study to the Research Ethics Committee for review. It is a pleasure to inform you the Ethics committee has formally approved the above mentioned study.

Please quote the REC. REF in all your correspondence.

Yours sincerely

DR. M BLOCKMAN
CHAIRPERSON

Appendix C: IeDEA-SA ethics approval



UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research 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	23/5/2014

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 D: MPH study ethics approval

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • **Facsimile** [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

27 June 2014

HREC/REF: 420/2014

Dr M Davies
CIDER
School of Public Health & Family Medicine
Level 5
Falmouth Building
FHS

Dear Dr Davies

Project Title: A DESCRIPTION OF HIV EXPOSED UNINFECTED INFANTS IN THE IeDEA SOUTHERN AFRICA COHORT AND AN EXAMINATION OF GROWTH OUTCOMES (Masters-candidate-E Morden) sub-study -084/2006

Thank you 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 30 June 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.

We acknowledge that the following student:- Erna Morden is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Hrec/ref:420/2014

Appendix E: BMC Pediatrics author instructions[2]

Instructions for authors

Research articles

Criteria | Submission process | Preparing main manuscript text | Preparing illustrations and figures | Preparing tables | Preparing additional files | Style and language

Assistance with the process of manuscript preparation and submission is available from BioMed Central customer support team. See 'About this journal' for information about policies and the refereeing process. We also provide a collection of links to useful tools and resources for scientific authors on our page.

Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our Editorial Policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

Submission process

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

Please note that ***BMC Pediatrics*** levies an article-processing charge on all accepted Research articles; if the submitting author's institution is a BioMed Central member the cost of the article-processing charge may be covered by the membership (see About page for detail). Please note that the membership is only automatically recognised on submission if the submitting author is based at the member institution.

To facilitate rapid publication and to minimize administrative costs, ***BMC Pediatrics*** prefers online submission.

Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time; when users return to the site, they can carry on where they left off.

See below for examples of word processor and graphics file formats that can be accepted for the main manuscript document by the online submission system. Additional files of any type,

[2] http://www.biomedcentral.com/bmcpediatr/authors/instructions/researcharticle

such as movies, animations, or original data files, can also be submitted as part of the manuscript.

During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal, to elaborate on any issues relating to our editorial policies in the 'About ***BMC Pediatrics***' page, and to declare any potential competing interests. You will be also asked to provide the contact details (including email addresses) of potential peer reviewers for your manuscript. These should be experts in their field, who will be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past five years, should not be current collaborators, and should not be members of the same research institution. Suggested reviewers will be considered alongside potential reviewers recommended by the Editorial team, Editorial Advisors, Section Editors and Associate Editors.

Assistance with the process of manuscript preparation and submission is available from BioMed Central customer support team.

We also provide a collection of links to useful tools and resources for scientific authors on our Useful Tools page.

File formats

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
- Portable document format (PDF)
- TeX/LaTeX (use BioMed Central's TeX template)
- DeVice Independent format (DVI)

TeX/LaTeX users: Please use BioMed Central's TeX template and BibTeX stylefile if you use TeX format. During the TeX submission process, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by internal staff as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF.

For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

Publishing Datasets

Through a special arrangement with LabArchives, LLC, authors submitting manuscripts to BMC Pediatrics can obtain a complimentary subscription to LabArchives with an allotment of 100MB of storage. LabArchives is an Electronic Laboratory Notebook which will enable scientists to share and publish data files in situ; you can then link your paper to these data. Data files linked to published articles are assigned digital object identifiers (DOIs) and will remain available in perpetuity. Use of LabArchives or similar data publishing services does not replace preexisting data deposition requirements, such as for nucleic acid sequences, protein sequences and atomic coordinates.

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Preparing main manuscript text

General guidelines of the journal's style and language are given below.

Overview of manuscript sections for Research articles

Manuscripts for Research articles submitted to ***BMC Pediatrics*** should be divided into the following sections (in this order):

- Title page
- Abstract
- Keywords
- Background
- Methods
- Results and discussion
- Conclusions
- List of abbreviations used (if any)
- Competing interests
- Authors' contributions
- Authors' information
- Acknowledgements
- Endnotes
- References
- Illustrations and figures (if any)
- Tables and captions
- Preparing additional files

The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database (EMBL), DNA Data Bank of Japan (DDBJ), GenBank at the NCBI (GenBank), Protein Data Bank (PDB), Protein Information Resource (PIR) and the Swiss-Prot Protein Database (Swiss-Prot).

You can download a template (Mac and Windows compatible; Microsoft Word 98/2000) for your article.

For reporting standards please see the information in the About section.

Title page

The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

Abstract

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background,** the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your research article reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

Keywords

Three to ten keywords representing the main content of the article.

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The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

Methods

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see 'About this journal'.

For further details of the journal's data-release policy, see the policy section in 'About this journal'.

Results and discussion

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

Conclusions

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

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A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

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Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

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We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

Authors' information

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Acknowledgements

Please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission.

Only articles, datasets, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited; unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited

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Article within a journal
Koonin EV, Altschul SF, Bork P: **BRCA1 protein products: functional motifs.*Nat Genet*** 1996, **13:**266-267.

Article within a journal supplement
Orengo CA, Bray JE, Hubbard T, LoConte L, Sillitoe I: **Analysis and assessment of ab initio three-dimensional prediction, secondary structure, and contacts prediction.*Proteins*** 1999, **43**(Suppl 3):149-170.

In press article
Kharitonov SA, Barnes PJ: **Clinical aspects of exhaled nitric oxide.*Eur Respir J***, in press.

Published abstract
Zvaifler NJ, Burger JA, Marinova-Mutafchieva L, Taylor P, Maini RN: **Mesenchymal cells, stromal derived factor-1 and rheumatoid arthritis [abstract].*Arthritis Rheum*** 1999, **42:**s250.

Article within conference proceedings
Jones X: **Zeolites and synthetic mechanisms.** In ***Proceedings of the First National***

Conference on Porous Sieves: 27-30 June 1996; Baltimore. Edited by Smith Y. Stoneham: Butterworth-Heinemann; 1996:16-27.

Book chapter, or article within a book
Schnepf E: **From prey via endosymbiont to plastids: comparative studies in dinoflagellates.** In ***Origins of Plastids. Volume 2.*** 2nd edition. Edited by Lewin RA. New York: Chapman and Hall; 1993:53-76.

Whole issue of journal
Ponder B, Johnston S, Chodosh L (Eds): **Innovative oncology.** In ***Breast Cancer Res*** 1998, **10:**1-72.

Whole conference proceedings
Smith Y (Ed): ***Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore.*** Stoneham: Butterworth-Heinemann; 1996.

Complete book
Margulis L: ***Origin of Eukaryotic Cells.*** New Haven: Yale University Press; 1970.

Monograph or book in a series
Hunninghake GW, Gadek JE: **The alveolar macrophage.** In ***Cultured Human Cells and Tissues.*** Edited by Harris TJR. New York: Academic Press; 1995:54-56. [Stoner G (Series Editor): ***Methods and Perspectives in Cell Biology,*** vol 1.]

Book with institutional author
Advisory Committee on Genetic Modification: ***Annual Report.*** London; 1999.

PhD thesis
Kohavi R: **Wrappers for performance enhancement and oblivious decision graphs.*PhD thesis.*** Stanford University, Computer Science Department; 1995.

Link / URL
The Mouse Tumor Biology Database [http://tumor.informatics.jax.org/mtbwi/index.do]

Link / URL with author(s)
Corpas M: **The Crowdfunding Genome Project: a personal genomics community with open source values** [http://blogs.biomedcentral.com/bmcblog/2012/07/16/the-crowdfunding-genome-project-a-personal-genomics-community-with-open-source-values/]

Dataset with persistent identifier
Zheng, L-Y; Guo, X-S; He, B; Sun, L-J; Peng, Y; Dong, S-S; Liu, T-F; Jiang, S; Ramachandran, S; Liu, C-M; Jing, H-C (2011): **Genome data from sweet and grain sorghum (Sorghum bicolor)**. ***GigaScience Database***. http://dx.doi.org/10.5524/100012.

Clinical trial registration record with persistent identifier
Mendelow, AD (2006): **Surgical Trial in Lobar Intracerebral Haemorrhage**. Current Controlled Trials. http://dx.doi.org/10.1186/ISRCTN22153967

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Additional file formats

Ideally, file formats for additional files should not be platform-specific, and should be viewable using free or widely available tools. The following are examples of suitable formats.

- Additional documentation
  - PDF (Adode Acrobat)
- Animations
  - SWF (Shockwave Flash)
- Movies
  - MP4 (MPEG 4)
  - MOV (Quicktime)
- Tabular data
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4. Access the index.html file and browse around the mini-website, to ensure that the most commonly used browsers (Internet Explorer and Firefox) are able to view all parts of the mini-website without problems, it is ideal to check this on a different machine.
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Style and language

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There is no explicit limit on the length of articles submitted, but authors are encouraged to be concise.

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advised to write clearly and simply, and to have their article checked by colleagues before submission. In-house copyediting will be minimal. Non-native speakers of English may choose to make use of a copyediting service.

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The abstract is one of the most important parts of a manuscript. For guidance, please visit our page on Writing titles and abstracts for scientific articles.

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Abbreviations

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Typography

- Please use double line spacing.
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- Use hard returns only to end headings and paragraphs, not to rearrange lines.
- Capitalize only the first word, and proper nouns, in the title.
- All lines and pages should be numbered. Authors are asked to ensure that line numbering is included in the main text file of their manuscript at the time of submission to facilitate peer-review. Once a manuscript has been accepted, line numbering should be removed from the manuscript before publication. For authors submitting their manuscript in Microsoft Word please do not insert page breaks in your manuscript to ensure page numbering is consistent between your text file and the PDF generated from your submission and used in the review process.
- Use the ***BMC Pediatrics*** reference format.
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Units

SI units should be used throughout (liter and molar are permitted, however).

Appendix F: Manuscript supplementary material

The tables below detail linear regression models including parity, maternal age and CD4 cell count. The number of dyads included is reduced compared to the models previously presented owing to incomplete data.

In addition, the same linear regression models were conducted for normal weight infants only. The effects in normal weight infants remain constant when contrasted with all infants, except for reduced effect magnitude.

Table 4 Longitudinal linear regression weight-for-age z-scores 0-28 weeks including parity and maternal CD4 (all infants, n=1387)

	unadjusted			*adjusted*		
variables	**unadjusted ß**	**95% CI**	**p-value**	**adjusted ß**	**95% CI**	**p-value**
any breastfeeding	0			0		
formula feeding	0.194	-0.048; 0.436	0.116	1.050	-0.510; 1.599	*
formula feeding x age	0.019	0.008; 0.030	0.001	-0.053	-0.084; -0.022	0.001
unknown feeding	-0.063	-0.422; 0.295	0.730	0.338	0.021; 0.655	0.037
unknown feeding x age	0.002	-0.016; 0.020	0.840	-0.033	-0.055; -0.011	0.004
birth weight ≥2500g	0			0		
birth weight <2500g	-2.303	-2.445; -2.160	*	-2.293	-2.437; -2.150	*
birth weight <2500g x age	0.055	0.043; 0.067	*	0.055	0.0419; 0.067	*
age (weeks)	0.034	0.028; 0.037	*	0.025	0.012; 0.038	*
parity = 0	0			0		
parity = 1	0.222	0.062; 0.383	0.006	0.213	0.081; 0.346	0.002
parity = 1 x age	-0.013	-0.024; -0.003	0.016	-0.013	-0.024; -0.002	0.02
parity = 2	0.088	-0.061; 0.248	0.278	0.193	0.050; 0.336	0.008
parity = 2 x age	-0.012	-0.023; -0.001	0.028	-0.012	-0.024; -0.0002	0.046
CD4 ≥500	0			0		
CD4 <200	-0.317	-0.506; -0.128	0.001	-0.107	-0.260; 0.046	0.169
CD4 <200 x age	0.009	-0.004; 0.022	0.174	0.007	-0.006; 0.020	0.270
200 < CD4 < 500	-0.047	-0.190; 0.096	0.518	0.042	-0.073; 0.157	0.475
200 < CD4 < 500 x age	0.006	-0.004; 0.016	0.234	0.003	-0.006; 0.012	0.533
Male sex	0			0		
Female sex	-0.160	-0.282; -0.039	0.010	0.021	-0.078; 0.119	0.679
Female sex x age	0.016	0.008; 0.024	*	0.012	0.003; 0.020	0.006
25-35 years[¶]	0			0		
young mother	-0.026	-0.181; 0.130	0.746	-0.005	-0.139; 0.128	0.936
young mother x age	-0.003	-0.014; 0.009	0.593	-0.008	-0.019; 0.003	0.161
older mother	-0.233	-0.395; -0.072	0.005	-0.089	-0.224; 0.045	0.193
older mother x age	-0.002	-0.013; 0.009	0.749	-0.004	-0.015; 0.007	0.474
Any ARVs	0			0		
no ARVs	-0.356	-0.652; -0.60	0.018	-0.045	-0.285; 0.194	0.711
no ARVs x age	-0.009	-0.031; 0.013	0.418	-0.012	-0.033; 0.010	0.279
ARVs missing information	-0.182	-0.732; 0.368	0.517	0.022	-0.417; 0.461	0.921
ARVs missing information x age	-0.028	-0.059; 0.004	0.083	-0.021	-0.051; 0.010	0.189

*p<0.0001

Table 5 Longitudinal linear regression, weight-for-age z-scores among normal birth weight infants

	Model including parity ; n=1953						*Model including all infants; n=2171*					
	unadjusted			*adjusted*			*unadjusted*			*adjusted*		
variables	**unadjusted ß**	**95% CI**	**p-value**	**adjusted ß**	**95% CI**	**p-value**	**unadjusted ß**	**95% CI**	**p-value**	**adjusted ß**	**95% CI**	**p-value**
any breastfeeding	0			0			0			0		
formula feeding	0.067	-0.090; 0.223	0.403	0.616	0.096; 1.136	0.020	0.031	-0.081; 0.143	0.591	0.083	-0.302; 0.468	0.672
formula feeding x age	0.024	0.016; 0.033	*	-0.057	-0.086; -0.029	*	0.023	0.017; 0.029	*	-0.032	-0.051; -0.012	0.002
unknown feeding	-0.126	-0.395; 0.143	0.358	0.108	-0.200; 0.416	0.491	-0.065	-0.321; 0.191	0.618	0.017	-0.269; 0.302	0.910
unknown feeding x age	0.003	-0.011; 0.018	0.646	-0.038	-0.058; -0.018	*	0.002	-0.012; 0.016	0.778	-0.029	-0.046; -0.012	0.001
age (weeks)	0.022	0.019; 0.026	*	0.014	0.007; 0.022	*	0.025	0.023; 0.028	*	0.011	0.007; 0.016	*
Male sex	0			0			0					
Female sex	0.040	-0.041; 0.121	0.336	0.038	-0.043; 0.119	0.357	0.043	-0.033; 0.120	0.267	0.042	-0.034; 0.118	0.278
Female sex x age	0.015	0.008; 0.021	*	0.015	0.009; 0.022	*	0.011	0.006; 0.017	*	0.012	0.007; 0.018	*
parity = 0	0			0			ǂ			ǂ		
parity = 1	0.160	0.054; 0.266	0.003	0.149	0.044; 0.254	0.005	ǂ			ǂ		
parity = 1 x age	-0.005	-0.013; 0.004	0.261	-0.001	-0.009; 0.007	0.772	ǂ			ǂ		
parity = 2	0.187	0.080; 0.294	0.001	0.164	0.057; 0.271	0.003	ǂ			ǂ		
parity = 2 x age	-0.015	-0.023; -0.006	0.001	-0.008	-0.017; 0.0004	0.063	ǂ			ǂ		

*p<0.0001 ǂNot included in the model

Table 6 Longitudinal linear regression weight-for-age z-scores 0-28 weeks including parity and maternal CD4 (normal birth weight infants, n = 1202)

	unadjusted			*adjusted*		
variables	**unadjusted ß**	**95% CI**	**p-value**	**adjusted ß**	**95% CI**	**p-value**
any breastfeeding	0			0		
formula feeding	0.014	-0.181; 0.208	0.889	0.818	0.219; 1.417	0.007
formula feeding x age	0.028	0.017; 0.040	*	-0.077	-0.113; -0.042	*
unknown feeding	-0.104	-0.414; 0.205	0.509	0.273	-0.088; 0.633	0.138
unknown feeding x age	0.005	-0.013; 0.024	0.561	-0.053	-0.078; -0.038	*
birth weight ≥2500g	‡			‡		
birth weight <2500g	‡			‡		
birth weight <2500g x age	‡			‡		
age (weeks)	0.025	0.021; 0.030	*	0.023	0.009; 0.037	*
parity = 0	0			0		
parity = 1	0.232	0.096; 0.368	0.001	0.217	0.078; 0.357	0.002
parity = 1 x age	-0.017	-0.028; -0.006	0.003	-0.014	-0.026; -0.003	0.016
parity = 2	0.201	0.064; 0.338	0.004	0.193	0.040; 0.346	0.013
parity = 2 x age	-0.018	-0.029; -0.006	0.002	-0.011	-0.024; 0.001	0.082
CD4 ≥500	0			0		
CD4 <200	-0.141	-0.306; 0.023	0.093	-0.159	-0.323; 0.004	0.056
CD4 <200 x age	0.009	-0.005; 0.023	0.197	0.012	-0.014; 0.026	0.079
200 < CD4 < 500	0.013	-0.107; 0.134	0.831	0.008	-0.112; 0.128	0.897
200 < CD4 < 500 x age	0.004	-0.006; 0.014	0.399	0.004	-0.006; 0.134	0.449
Male sex	0			0		
Female sex (sex)	0.010	-0.095; 0.114	0.856	0.006	-0.098; 0.110	0.908
sex x age	0.013	0.004; 0.022	0.004	0.014	0.005; 0.023	0.002
25-35 years¶	0			0		
young mother	-0.087	-0.218; 0.045	0.197	-0.004	-0.144; 0.137	0.956
young mother x age	-0.002	-0.013; 0.009	0.759	-0.010	-0.022; 0.002	0.108
older mother	-0.111	-0.253; 0.031	0.127	-0.123	-0.270; 0.023	0.100
older mother x age	-0.005	-0.017; 0.006	0.365	-0.004	-0.016; 0.008	0.503
Any ARVs	0			0		
no ARVs	0.024	-0.253; 0.300	0.866	0.023	-0.252; 0.298	0.870
no ARVs x age	-0.032	-0.058; -0.006	0.014	-0.030	-0.055; -0.003	0.028
ARVs missing information	0.270	-0.228; 0.767	0.288	0.231	-0.262; 0.724	0.359
ARVs missing information x age	-0.033	-0.065; -0.0002	0.049	-0.024	-0.056; 0.008	0.143

*p<0.0001 ‡Not included in the model