Social and contextual factors affecting HIV-infected women's feeding practices for their infants in normal practice settings – effects on growth and morbidity

by

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Summary

Background: Studies showing that breastfeeding protects against infectious morbidity and the significant reduction in HIV transmission through breastfeeding by antiretroviral treatment guided the current recommendations favouring breastfeeding which has to be continued until 12 months of age. Infant feeding guidelines for HIV-infected women in low-resourced settings are primarily informed by studies that spend much effort in controlling guideline adherence by investigators and participants. These studies however may not reflect the real world effects of the feeding options on important outcomes because such efforts are less enforced or rear in primary care settings. Reliable studies are lacking for predicting the real world effects of the feeding options on infant growth and morbidity to guide healthcare authorities in decision making. Social and contextual factors affecting HIV-infected women's infant feeding practices are major barriers to uptake of infant feeding recommendations to levels that would result in a significant impact. Yet less attention is paid to these during guideline development and implementation. Methods: To address this knowledge gap we performed a longitudinal cohort study in primary healthcare settings, over a 12 months period. The objectives were to a) describe HIV-infected women's infant feeding practices b) compare infant feeding practices of HIV-infected and HIV-uninfected breastfeeding women c) assess growth and infection-related hospitalizations among predominantly breastfed and predominantly formula-fed HIV-exposed uninfected infants. We explored infant feeding experiences of a sub-set of HIV-infected women who were followed-up for at least 6 months post-delivery in the longitudinal cohort. Results: We found that few HIV-infected women chose breastfeeding, and among those who did, many switched to formula feeding early. The proportion of women who continued predominantly breastfeeding was only slightly lower among HIV-infected compared to HIV-uninfected women (p = 0.0005). These differences were seen from about two weeks, and persisted throughout follow-up. By about four months, half of the HIV-infected women had switched to predominant formula feeding. However, the proportion of HIV-uninfected women who switched to formula feeding was also relatively high. The dual infant feeding option employed by the Western Cape PMTCT program while transitioning from formula feeding policy confused HIV-infected women who were worried that their child may contract HIV through breastmilk because of conflicting messages they received from healthcare providers, possibly explaining why some women stopped breastfeeding. Women's interpretation of information about risks and benefits of infant feeding options, formula feeding stigma and the quality of infant feeding counselling affected women's infant feeding practices. Mean weight velocity Z-scores (95% CI) of predominantly breastfed infants was -0.70 (-1.31 to -0.09; p = 0.024) lower than that of predominantly formula fed infants in the two to four months age interval. Protection against infections by

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breastfeeding was minimal and insignificant, odds ratio (OR) 0.95 (95% CI 0.33 to 2.74). In conclusion, it is important that all women, whether HIV-infected or not, be educated that breastfeeding is the feeding of choice in this setting. The potential of breastfeeding to reduce risks of infections to levels similar to those observed under highly controlled settings, involves changing women's infant feeding practices. Strategies to promote and sustain continued breastfeeding by women, to levels that would result in a significant impact on the growth and protection against infections of their children are urgently needed. The strategies should be guided by social and contextual factors affecting women's feeding practices.

Opsomming

Studies toon aan dat borsvoeding beskermend is teen aansteeklike morbiditeit en ook 'n betekenisvolle verlaging in MIV oordrag deur borsvoeding en anti-retrovirale behandeling (ARB). Hierdie feite het daartoe aanleiding gegee tot die huidge aanbevelings van borsvoeding as voorkeur tot op 12 maande te gee. Babavoedingriglyne vir MIV-geïnfekteerde vroue in lae-inkomste omgewings word primêr gedryf deur studies wat daarin poog vir die riglynbeheer toepassing deur navorsers en deelnemers. Hierdie studies mag nie noodwendig die werklikheid van voedingsopsies ten opsigte van belangrike uitkomste lewer nie omrede verskeie pogings tot 'n mindere mate toegepas en selfs raar is in primêre gesondheidsorgomgewings. Daar bestaan 'n leemte in betroubare studies wat die werklikheidseffekte van voedingsopsies op babagroei en morbiditeit voorspel, en wat daarin poog om gesondheidsorg owerhede se besluitneming te kan beïnvloed. Sosiale en kontekstuele faktore wat MIV-geïnfekteerde vroue se babavoedings keuses beïnvloed, is die hoof hindernis om babavoedingaanbevelings deur te voer wat 'n betekenisvolle impak sal maak. Minder aandag word aan hierdie aspekte tydens die riglynontwikkeling en implementering spandeer. Om die kennisgaping romdom hierdie aspek te adreseer het ons 'n longitudinale studie in primêre gesondheidsorgeenhede oor 'n 12 maande periode ondersoek. Die doelstellings was om a) MIV-geïnfekteerde vroue se babavoedingkeuses te beskryf b) babavoedingpraktyke van MIV-geïnfekteerde vroue en MIV-nie-geïnfekteerde borsvoedende vroue te vergelyk c) groei en infeksie-verwante hospitalisasies onder hoofsaaklik borsvoedende en formule voedende MIV-blootgestelde ongeïnfekteerde babas in primêre gesondheidsorgomgewings oor 'n 12 maande periode te evalueer. Ons het babavoedingervarings in 'n sub-groep MIV-geïnfekteerde vroue vir ses maande na bevalling in die longitudinale kohort ondersoek. Resultate: Ons het gevind dat min MIV-geïnfekteerde vroue borsvoeding gekies het, en onder die wat wel het, baie vroeg oorgeskakel het na formule voeding. Die aantal vroue wat hoofsaaklik by borsvoeding gehou het is betekenisvol minder onder die MIV-geïnfekteerde as die ongeïnfekteerde vroue (p = 0.0005). Hierdie verskille is sigbaar teen omtrent twee weke en is regdeur die opvolg waargeneem. Om en by vier maande het die helfte van die MIV-geïnfekteerde vroue na hoofsaaklik formule voeding oorgeskakel. Die gedeelte van die MIV-geïnfekteerde vroue wat oorgeskakel het na formule voeding was ook relatief hoog. Die dubbel babavoedingopsie, wat deur die Weskaapse PMTCT program as opsie gegee word in die oorgangsfase van formule voeding, het MIV-geïnfekteerde moeders verwar omrede hulle bekommerd was dat hulle kinders deur borsmelk MIV mag opdoen weens teenstrydige boodskappe wat hulle van gesondheidswerkers ontvang het, kan moontlik verklaar waarom sommige vroue ophou

borsvoed het. Die vroue se interpretasie van die inligting oor risikos en voordele van babavoedingsopsies, formule voedingstigma en die kwaliteit van voedingsberading, het die moeders se voedingskeuses beïnvloed. Gemiddelde massa snelheid Z-tellings (95% VI) van die meerderheid borsvoedende moeders was -0.70 (-1.31 to -0.09; p=0.024) laer as die van die meerderheid formule gevoede babas in die twee tot vier maande ouderdomsinterval. Vroue wat formulevoeding gegee het, het verhoogde persepsies oor MIV oordragrisiko deur borsmelk gehad. Teen ses maande ouderdom, het hoofsaaklik borsgevoede babas gewig teen 'n tempo van 0.08 (95% vertrouheidsinterval (VI): -0.14 tot -0.02; p = 0.01) opgetel, gewig-vir-ouderdom z-tellings per maand was laer as in die hoofsaaklik formule gevoede babas. Beskerming teen infeksies deur borsvoeding was minimaal en nie betekenisvol nie, kansverhouding (KV) 0.95 (95% VI 0.33 tot 2.74). Gevolglik, is dit belangrik dat alle vroue, ongeag of hulle met die MIV geïnfekteer is of nie, opgevoed te word dat borsvoeding die voeding van keuse is in hierdie omgewing. Strategieë om borsvoeding deur vroue te bevorder, en wat tot betekenisvolle impak op die groei en beskerming teen aansteeklike siektes van hulle kinders voort te sit, is uiters noodsaaklik. Die strategieë behoort deur sosiale en kontekstuele faktore gerig te word wat vroue se voedingskeuses beïnvloed.

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List of abbreviations

3TC	Lamivudine
AFASS	Acceptable, Feasible, Affordable, Sustainable, Safe
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral treatment
ARV	Antiretroviral
AZT	Zidovudine
BAN	Breastfeeding, Antiretrovirals and Nutrition
cART	Combination Antiretroviral treatment
CD4	Cluster of differentiation 4
CI	95% confidence interval
DNA	Deoxyribonucleic acid
EFV	Efavirenz
ELISA	enzyme-linked immunosorbent assay
FTC	Emtricitabine
HIV-1	Human Immunodeficiency Virus 1
HPTN	HIV Prevention Trials Network
IQA	Interactive qualitative analysis
KID-CRU	Children's Infectious Diseases Clinical Research Unit
LAZ	Length-for-age Z-scores
LTFU	Lost to follow-up
LVZ	Length velocity Z-scores
MTCT	Mother-to-child transmission
NVP	Nevirapine
OR	Odds ratio
PCR	Polymerase-chain-reaction assay
PEPI	Post-Exposure Prophylaxis of Infants
PI	Principal investigator
PMTCT	Prevention of mother-to-child transmission
RNA	ribonucleic acid
SD	Standard deviation
Sd-NVP	Single dose nevirapine
SE	Standard error
SIDs	System Influence Diagrams
SWEN	Six-Week Extended-Dose Nevirapine

TB	Tuberculosis
TDF	Tenofovir
WAZ	Weight-for-age Z-scores
WHO	World Health Organization
WLZ	Weight-for-length Z-scores
WVZ	Weight velocity Z-scores

Chapter 1

Introduction

Introduction

Since the discovery more than 30 years ago, that Human Immunodeficiency Virus (HIV) can be transmitted from an HIV-infected woman to her infant through breast milk, information has been accumulating to guide infant feeding practices for HIV-infected women in low-resourced settings. Feeding guidelines are informed primarily by evidence from tightly controlled studies evaluating the effects of alternative infant feeding options on important clinical outcomes. Most of these studies test the efficacy of the feeding interventions and also invest a lot of effort into controlling guidelines adherence of practitioners and participants. The limitation of such studies is that the findings may not reflect what happens in real world settings, where the same level of effort for ensuring adherence is rare.

Background

Previous studies support breastfeeding in minimizing the risks of respiratory and gastrointestinal infections, and also malnutrition (1). Exclusive breastfeeding for 6 months prevents about 1.3 million (13%) child deaths per year for children less than 5 years, compared to formula feeding that prevents 150 000 (2%) of global child death (2). Breastfeeding for less than 6 months compared to breastfeeding for more than 6 months was associated with poor growth from 4 to 24 months in a randomized controlled trial in Zambia (3).

Prevention of mother-to-child HIV transmission programs (PMTCT) in low-resourced settings evaluated the effect of antiretroviral (ARV) interventions in reducing the risk of HIV transmission and making breastfeeding safe for HIV-infected women. Between 2006 and 2010, randomized controlled trials demonstrated a consistent effect of triple combination antiretroviral treatment (cART) given either to the HIV-infected woman or HIV-exposed infant in reducing HIV transmission during breastfeeding (4-7). These findings dramatically changed infant feeding recommendations for HIV-infected women in low-resourced settings, with the World Health Organization (WHO) recommending a standardised triple-drug regimen during pregnancy and the breastfeeding period, regardless of CD4 count (8,9). These recommendations have changed clinical practice even in low-resourced settings with high uptake of formula feeding and relatively low rates of breastfeeding by HIV-infected women, for example the PMTCT programs in Western Cape Province of South Africa are now recommending breastfeeding that has to be continued until 12 months.

Study justification

Studies evaluating the clinical effects of alternative infant feeding options were conducted under idealised conditions. Most of these studies devote much effort to controlling guideline adherence of practitioners and participants. In real world setting of implementation, the same effort of control is rare (10). We previously questioned whether the effects of infant feeding interventions from a randomized controlled trial and some tightly controlled observational studies could be extrapolated to normal practice settings (11). We previously conducted a systematic review to estimate the effects of breastfeeding, formula feeding and other infant feeding intervention on improving infant growth and reducing non-HIV infections (11) (see Appendix 1). I searched online databases, PubMed, SCOPUS, and Cochrane CENTRAL Controlled Trials Register for potential studies to include in the systematic review. Randomized trials and prospective cohort studies were included in the review. One co-author (GM) and I independently extracted data, evaluated risk of bias and assessed the quality of evidence of included studies. I also performed the meta-analysis. The review showed that breastfeeding HIV-exposed infants reduce the risk of diarrhoea and respiratory infections by about 26 and 35%, respectively, through two years of age. Breastfeeding tended to protect against malnutrition. We then questioned whether the evidence from this review of randomized controlled trials and some tightly controlled observational studies could be extrapolated to normal practice settings (11). We performed a longitudinal cohort study to address the question whether predominant breastfeeding compared to predominant formula feeding improves growth and reduces infectious morbidity of HIV-exposed uninfected infants in primary healthcare clinics.

Many PMTCT programs in low-resourced settings recently adopted "Option B+" strategy into policy, where HIV-infected women are put on triple-cART, irrespective of CD4 count, which has to be maintained at least for the duration of breastfeeding or as lifelong treatment. While the Option B+ strategy is a sound medical and public health approach, the shift in formula policy by Western Cape PMTCT program may not have put much consideration on social, and contextual issues affecting HIV-infected women infant feeding practices (12,13).

Scope of the research

We performed a longitudinal cohort study on the effects of predominant breastfeeding and predominant formula feeding on infant growth and infection-related hospitalizations, among HIV-exposed uninfected infants in real life primary healthcare settings. We also explored HIV-infected women's experiences and perceptions on breastfeeding and formula feeding during a time when the Western Cape PMTCT program was withdrawing provision of free formula milk and starting to provide all HIV-infected women with lifelong cART and promoting breastfeeding. The research findings are likely to reflect what happens to a larger

population of HIV-infected women and infants born to HIV-infected women, and could therefore inform infant feeding policy and practice for HIV-infected women in low-resourced settings.

Objectives
- o To describe HIV-infected women's infant feeding practices.
- o To determine the effect of predominant breastfeeding and predominant formula feeding on improving growth (weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ) z-scores) of HIV-exposed uninfected infants in primary healthcare settings, over 12 months.
- o To determine the effect of predominant breastfeeding and predominant formula feeding on growth velocity (weight velocity Z-scores (WVZ), length velocity Z-scores (LVZ)) of HIV-exposed uninfected infants in primary healthcare settings, during the first 6 months.
- o To determine the effect of predominant breastfeeding and predominant formula feeding on infection-related hospitalizations of HIV-exposed uninfected infants in primary healthcare settings, over 12 months.
- o To explore HIV-infected women's experiences and perceptions on breastfeeding and formula feeding during a time when the Western Cape PMTCT program was withdrawing provision of free formula milk and started providing all HI-infected women with lifelong cART and promoted breastfeeding.

Methods

We enrolled HIV-infected women and their exposed infants to assess the effect of predominant breastfeeding and predominant formula feeding on infant growth and infection-related hospitalizations over a 12 months period.

Women who gave birth between July 2012 and December 2013 at Kraaifontein Midwife Obstetric Unit, in Cape Town, South Africa, were invited to participate in the study. Women could participate if they were at least 16 years of age and delivered at the obstetric unit during weekday daytime hours. We evaluated only those women who were HIV-infected, had been on Zidovudine (AZT) for ≥ 2 weeks or on cART for ≥6 weeks before delivery; women who were pregnant with more than 1 infant were excluded. Infants were enrolled if they had a birth weight of at least 2000g and a gestational age of 36 weeks or more. Mother-infant pairs were followed for 12 months post-partum at the Children's Infectious Diseases Clinical Research Unit, in Tygeberg Academic Hospital. Final follow-up was completed in December 2014.

We compared growth (WAZ, LAZ, and WLZ z-scores), growth velocity (WVZ and LVZ) and infection-related hospitalizations of HIV-exposed uninfected infants who were predominantly breastfed and those who were predominantly formula fed.

We also explored HIV-infected women's experiences and perceptions on breastfeeding and formula feeding in a sub-sample of HIV-infected women who were followed-up for at least 6 months post-delivery in the longitudinal cohort. We used Interactive Qualitative Analysis methods (IQA); where HIV-infected women described, labelled their experiences, and articulated perceived relationships among their experiences.

The Human Research Ethics Committee of Stellenbosch University approved the main protocol and amendment protocol (Ref: S12/03/065). All participants provided a written informed consent for study participation.

Thesis outline
The thesis comprises 7 chapters. This chapter provides an overview to the reader.

Chapter Two provides a literature review of the study. A review on epidemiology and global burden of HIV/AIDS, and antiretroviral medication for treatment and prevention of HIV/AIDS is provided. Antiretroviral interventions for prevention of mother-to-child transmission of HIV and infant feeding policies for HIV-infected women in low-resourced settings are summarized.

Chapter Three: Part A outlines the study objectives and study hypotheses of the longitudinal cohort study. The cohort study design and methods employed to evaluate infant growth and infection-related hospitalizations outcomes are outlined.

Chapter Three: Part B outlines the study objectives of the qualitative sub-study. The IQA methods employed to explore HIV-infected women's experiences and perceptions on breastfeeding and formula feeding are described.

Chapter Four provides the findings and a discussion on effects of predominant breastfeeding and predominant formula feeding on growth and infectious morbidity of HIV-exposed uninfected infants.

Chapter Five provides the findings and a discussion of HIV-infected women's experiences and perceptions of their infant feeding practices.

Chapter Six gives a summary of the main findings, a conclusion and limitations of the study. It also highlights implications of study findings on clinical practice and future research.

Chapter 2

Literature Review

Epidemiology and global burden of HIV/AIDS

The first cases of Acquired Immunodeficiency Syndrome (AIDS) were described in 1981 among young homosexual men who presented with rare opportunistic infections and malignancies (14). A year later, in 1982, the first paediatric cases of AIDS were reported in infants whose mothers had risk factors for AIDS (15). In 1983-4, HIV-1, was identified as the cause of AIDS (16-18). By 1993, there was a dramatic increase in the number of people living with HIV infection globally estimated at 13 million (19). Subsequent global reports indicate an increase in the number of people living with HIV of approximately 5 million people per decade, with an estimate of 30 million in 2001, 34.9 million in 2011 and 35.3 million in 2012 (20).

The geographical distribution of the HIV epidemic varies. Sub-Saharan Africa carries the greatest burden (70.8%), with mostly young adults affected (20). Within sub-Saharan Africa, southern Africa is affected most with the majority of the 23.5 million people living with HIV in sub-Saharan Africa. South Africa had the highest HIV prevalence of 6.1 million people (20). South Africa's national antenatal HIV prevalence rate increased from 0.7% in 1990 to 29.5% in 2012 (21).

Epidemiological patterns for HIV infection in Africa are similar to elsewhere in the world. There are more HIV-infected men than women. The reason for unequal distribution between genders is unclear, a recent study attributed gender inequality to increased mortality among HIV infected men (31% higher) compared to women (22).

HIV infection contributes considerably to the global burden of disease. In 2010, disability-adjusted life years among young people (30-44 years) were primarily due to HIV (23). While global AIDS related deaths peaked at 2.3 million in 2005, a remarkable decrease to 1.6 million was reported in 2012 (20). Most (75%) of these deaths were from sub-Saharan Africa (20). The decreasing mortality can be attributed largely to the recent increased access to ART for HIV-infected people which has changed the epidemiology of HIV infection worldwide. About 10 million HIV-infected people in low-income and middle-income countries were on ART in 2012 (24), representing 61% of HIV-infected people eligible for treatment under the 2010 WHO HIV treatment guidelines (24). Access to treatment for people living with HIV/AIDS in low- and middle income countries saved over 4.2 million lives in 2002–2012 (24). However, with the revisions of the HIV treatment guidelines in 2013, the treatment

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coverage in low- and middle income countries represented roughly 34% of the 28.6 million people eligible for HIV treatment in that year (24). The global prevalence of HIV has increased from 31.0 million in 2002, to 35.3 million in 2012, because people on ART are living longer (20). A 30% reduction in global rates of new HIV infections (horizontal transmission); a decrease from 3.3 million in 2001, to 2.3 million in 2012 was associated with increased access to ART (20). More importantly, 26 countries, 16 being in sub-Saharan Africa, reported a reduction of new HIV infections of at least 50% between 2001 and 2012 (20). Despite these achievements, rates of new HIV infections remain high, with 70% occurring in sub-Saharan Africa (20).

HIV-1 transmission and risk factors

Human immunodeficiency virus type 1 is transmitted through sexual, percutaneous, and perinatal routes, with the former being most common (25,26). The main risk factor for sexual transmission of HIV-1 is the number of HIV-1 RNA copies (viral load) per mL of plasma. The risk increases by 2.4 for every 1 $\log_{10}$ increase in viral load (27). New HIV infection, associated with very high plasma viral loads, increases the risk of transmission (26). Other risk factors for sexual transmission of HIV include co-existing sexually transmitted diseases for example genital ulcers (28), herpes simplex type-2 (29), bacterial vaginosis (30) and pregnancy (31). Behavioural risk factors include many sexual partners (32,33).

Antiretroviral therapy for HIV treatment and prevention

Suppression of viral replication through cART has changed the poor prognosis of HIV/AIDS into a chronic manageable disease (34). HIV treatment guidelines in high-income countries recommend initial treatment with dual nucleoside reverse transcriptase inhibitors combined with either a non-nucleoside reverse transcriptase inhibitor, a ritonavir-boosted protease inhibitor, or an integrase inhibitor (35). Similarly, WHO HIV treatment guidelines for low- and middle-income countries recommend first-line ART consisting of two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (tenofovir (TDF), lamivudine (3TC) or emtricitabine (FTC), and efavirenz (EFV). Combinations with zidovudine (AZT) or nevirapine (NVP) are recommended as alternatives, in resource constrained settings (8,9).

Plasma viral load decreases to undetectable levels by commercial assay, within three months of starting ART in most people. However, recovery of CD4 T cells varies widely among people on ART. Tuboi et al., 2007 reported high variability in virological or CD4 responses to ART at 6 months; 56% had a successful virological and CD4 response, 19% and 15% had only virological and CD4 response, respectively (36). HIV-infected people with poor CD4 T-cell recovery regardless of successful virological suppression have a high risk for adverse outcomes, including serious non-AIDS events (37).

With improved access to ART and at higher CD4 counts, HIV-infected people will initiate ART early and live longer and therefore become increasingly susceptible to chronic diseases. About half of the deaths among HIV-infected people on ART in high-income countries are not associated with AIDS related disease (38). Main causes of non-AIDS-related deaths in these countries were non-AIDS defining cancers (23.5%), heart disease (15.7%), and liver disease (14.1%) (38). In contrast, tuberculosis is the main cause of morbidity and mortality among HIV-infected people in low- and middle-income countries, (39).

Several studies showed the effectiveness of antiretroviral interventions in reducing the spread of HIV at population level. Antiretroviral treatment was associated with a reduction in HIV incidence in an HIV-uninfected partner in the HIV prevention trials network (HPTN) 052 study (40). In the trial, the HIV-infected partner from a sero-discordant couple with CD4 counts of 350-550 cells per μL was randomly assigned to immediate or deferred ART (when CD4 count was <250 cells per μL). Compared to deferred ART immediate ART was associated with a 96% reduction in new HIV infections (40).

The public health impact of ART coverage was reported in a rural setting with high HIV prevalence, KwaZulu Natal, South Africa (41). Communities with high ART coverage (defined as 30-40% among all HIV-infected people) had a 38% lower risk of getting HIV infection compared to communities with ART coverage of less than 10% (41). A mathematical model assessing the impact of universal HIV testing and immediate ART for all HIV-infected people, predicted a reduction in both HIV incidence and mortality of less than 1 case per 1000 people per year within 10 years of implementing the strategy, and a reduction in HIV prevalence of to less than 1% within 50 years (42).

As evidence accumulated that starting ART early delays HIV disease progression, the WHO revised the ART guidelines in 2013 recommending that ART be started in HIV-infected people with WHO clinical stage 1 or 2 and a CD4 count ≤ 500 cells/mm^3 and people with severe or advanced HIV infection (WHO clinical stage 3 or 4), irrespective of CD4 cell count (43). Although ART has reduced HIV transmission and AIDS related deaths, access is not universal, especially in low-income countries (20), and the development of vaccines or treatments that cure HIV remain uncertain (44,45). Thus, HIV/AIDS will remain a public health issue and of concern for paediatric HIV infections for years to come.

Prevention of postnatal mother-to-child-transmission of HIV infection through breast-milk

Infant feeding for HIV–infected women in low-resourced settings
A series of case reports in 1985-88 provided the first evidence that HIV could be transmitted from an HIV-infected mother to her infant through breast milk (46-48). Both HIV infection and infant feeding became important public health issues especially in low-resourced settings, where breastfeeding has been associated with child survival (49,50).

Cumulative rates of mother-to-child HIV transmission (MTCT) reflect transmission during pregnancy, delivery, or post-delivery through breast milk (51). In non-breastfed infants, about 30% of HIV infections occur during pregnancy, with the majority (70%) occurring during labour and delivery (52,53). HIV transmission rates from an HIV-infected mother to her formula fed infant, with no treatment ranged from 14-32% in high-income countries compared to 25-48% among infants in low-income countries who are mostly breastfed (54). With no ART, the risk of HIV transmission is about 1.57% per month of breastfeeding when maternal CD4 count is low (<350 cell/ml) versus 0.51% when maternal CD4 count is higher (55). This converts to a cumulative postnatal HIV transmission risk of 14-20% at 2 years of age, among infants of HIV-infected mothers. New HIV infection increases the postnatal transmission risk to about 28% irrespective of the duration of breastfeeding (56).

As early as 1992, high-income countries had settled on an infant feeding policy for HIV-infected women, where avoidance of breastfeeding and use of safe alternatives was recommended (57). Following use of ART, caesarean section and formula milk, MTCT of HIV was reduced to below 2% in high-income countries (58). In 2001, the WHO recommended formula feeding for HIV-infected women in low-resourced settings based on experiences from high-income countries (59). The guidelines recommended formula feeding on condition that it is acceptable, feasible, affordable, sustainable and safe (AFASS criteria). Exclusive breastfeeding was recommended as an alternative when the AFASS criteria were not met (59). HIV-infected women who chose to exclusively breastfeed on discontinuation of breastfeeding had to stop abruptly within the first 4-6 months. However, the drawback of rapid weaning was increased risk of infant morbidity.

At the end of 2005 about 2.3 million children less than 15 years of were living with HIV, 700,000 new infections were reported in children, mostly through MTCT and 570,000 AIDS associated deaths were reported (60). The urgency for preventing new HIV infections in children in low-income countries grew. In 2005, the Inter-Agency Task Team on prevention of mother-to-child transmission (PMTCT) and Paediatric HIV brought together governments, donors and partners to the PMTCT Global Partners Forum in Abuja, Nigeria (61). A call to eliminate HIV infection in infants and children was made (61). In late 2005, Joint United

Nations Programme on HIV/AIDS and United Nations Children Fund launched a campaign supporting universal access to treatment and assessment of the impact of HIV/AIDS on children (62).

After 2001, a number of studies conducted among breastfed and non-breastfed infants showed efficacy of short course antiretroviral drug combination given during pregnancy and post-delivery in reducing the risk of MTCT of HIV. The short course antiretroviral combinations included AZT + 3TC (63-65), AZT + single dose nevirapine (Sd-NVP) (66-68), or AZT and 3TC + Sd-NVP (67). Based on these findings the WHO updated infant feeding guidelines in 2006 (69). The principles of the guidelines were similar to those of the 2001 guidelines. HIV-infected women were recommended to get either ART or prophylaxis to prevent MTCT, depending on whether they had indications for ART for their own health (69). The guidelines specified how the recommended regimens were to be taken during pregnancy, delivery, and post-delivery. Infant feeding option for HIV-infected women considered the individual situations of the woman, which included woman's health status, and health services available. Both 2001 and 2006 guidelines recommended avoidance of breastfeeding if the AFASS criteria were met, otherwise HIV-infected women had to exclusively breastfeed for the first six months.

Overwhelming evidence supports breastfeeding in reducing infant morbidity and mortality in resource-poor settings, by minimizing the risks of respiratory and gastrointestinal infections and also malnutrition (1). About 1.3 million (13%) child deaths per year of children less than 5 years are prevented, if most (90%) of infants less than 6 months are exclusively breastfed, whereas, avoidance of breastfeeding prevents 150 000 (2%) of global child death (2). Important findings were reported in a study in South Africa, where exclusive breastfeeding up to six months reduced MTCT of HIV rate to 4%, (70). The same study reported lower mortality rates in exclusively breastfed infants (6.1%) compared to formula fed infants (15.1%) (70). In addition, breastfeeding for less than 6 months was associated with increased infant mortality and poor growth from 4 to 24 months in a randomised controlled trial in Zambia (3). Another study showed a reduction in infant survival when women shortened the duration of breastfeeding (71).

The major drawbacks of the 2001 and 2006 WHO infant feeding guidelines were that most HIV-infected women in low-resourced settings could not meet the criteria to formula feed. Few research findings showed that formula feeding reduced mortality and improved HIV-free survival among HIV-exposed infants in low resourced settings (72). The need to develop ART interventions that reduce the risk of HIV transmission through breast milk was realised.

Antiretroviral interventions to reduce HIV transmission through breast milk

Studies were conducted in low-resourced settings between 2006 and 2010 with ART given either to the HIV-exposed infant or HIV-infected woman, for a longer duration, to reduce the risk of HIV transmission through breast milk. These included the Breastfeeding, Antiretrovirals and Nutrition (BAN), Post-Exposure Prophylaxis of Infants (PEPI) (7,73,74), Six-Week Extended-Dose Nevirapine (SWEN) (75), and HIV Prevention Trials Network (HPTN 046) (76) trials. In 2008, the SWEN study reported a 0.54 risk reduction of HIV transmission in HIV-exposed infants receiving a 6 week regimen of daily NVP compared to infants receiving a single dose of NVP (75). Kumwenda et al., reported similar findings in 2008 (77). HIV-exposed infants were randomly assigned to one of the three regimens; Sd-NVP plus 1 week of AZT (control regimen) or the control regimen plus daily extended prophylaxis either with NVP (extended NVP) or with NVP and AZT (extended dual prophylaxis) until the age of 14 weeks (77). At 9 months, HIV-1 infection was 10.6% in the control group, 5.2% in the extended-NVP group (p<0.001) and 6.4% in the extended-dual-prophylaxis group (p = 0.002) (77). In HPTN 046, NVP given to infants until 6 months of age almost halved HIV infection rates between 6 weeks and 6 months compared to placebo (1.1% versus 2.4%) (76). The study also reported a reduction in risk of HIV transmission through breast milk among women on lifelong ART for their own health, irrespective of whether their infants had received NVP or placebo (76). Women's CD4 count was a significant risk factor of postnatal HIV transmission through breast milk (76). The study reported similar HIV transmission rate of about 1% among infants (on NVP) of women on lifelong ART for their own health and infants of women not on lifelong ART with high CD4 count (at least 350 cells/ml) (76).

Following the success of triple-cART in reducing the risk of MTCT during pregnancy and labour to below 2% in high-income countries (78-80), low-income countries started evaluating the effect of triple-cART in reducing the risk of postnatal MTCT of HIV through breast milk. The MmaBana and Kesho Bora studies found very low HIV transmission rates through breast milk, irrespective of HIV-infected women's eligibility for lifelong cART for their own health (4,5). The Mitra and BAN studies reported similar findings with extended infant antiretroviral prophylaxis or maternal triple-cART (6,81).

Triple-cART reversed the increasing trend of the paediatric HIV infections in low-resourced settings. A decrease of 38% in new paediatric HIV infections, between 2009 and 2012 was associated with improved ART access for PMTCT (24). Over 900 000 HIV-infected pregnant women were on ART at the end of 2012, worldwide (24). Antiretroviral treatment coverage in PMTCT programs increased from 59% in 2011 to 62% in 2012, in 22 priority countries, which are home to about 90% of pregnant women with HIV, globally (24). Botswana, Ghana,

Namibia and Zambia are among other countries already providing ART to the majority (90%) of HIV-infected pregnant women. However, antiretroviral coverage was lower during the breastfeeding period (49%) than during pregnancy and delivery (62%) in 2012 (24). Nevertheless, because of increased access to cART for PMTCT in low-resourced settings, only 260 000 children were newly infected in 2012, 35% lower than in 2009 (20).

The infant feeding guidelines for low-resourced settings were further revised to minimise the risk of HIV transmission based on studies that had shown that cART or prophylaxis given either to the woman or her infant reduce the risk of HIV infection through breast milk. The WHO guidelines of 2010 and 2013 took into consideration provision of cART to the HIV-infected woman either for a recommended period or for life, respectively (8,9). The current guideline (WHO 2013) (9), recommends triple-cART, irrespective of woman's CD4 count, which has to be maintained at least for the duration of breastfeeding or as lifelong treatment, also called "Option B+" (9).

The infant feeding guidelines for HIV-infected women in low-resourced settings evolved from no breastfeeding to breastfeeding with rapid weaning at 4-6 months and now, breastfeeding for at least 1 year with triple-cART covering the pregnancy, delivery and post-delivery MTCT risk period. The feeding guidelines for HIV-infected women in low-resourced settings are informed primarily by evidence from an explanatory randomized controlled trial (116) and tightly controlled observational studies. These studies evaluated the effects of alternative infant feeding options for HIV-infected women, on infant growth and morbidity, under tightly controlled conditions (11). Most of these studies devote much effort to controlling guideline adherence of investigators and participants.

What is known in the South African context?
An ongoing debate issued among those supporting and those against breastfeeding for HIV-infected women, because of the confusion around the risk of HIV transmission through breast milk. Two aspects complicated this situation further. Firstly, in most communities in low-resourced settings, breastfeeding is a symbol of good motherhood; and the second aspect relates to the commercial interests of food industries that are likely to benefit from promoting formula feeding (82).

The South African PMTCT program adopted the 2010 WHO guidelines (83). At the time, however, the guidelines promoted both exclusive breastfeeding and formula feeding. Healthcare authorities from different provinces differed on the feeding option they supported, with most provinces supporting exclusive breastfeeding and a few supporting formula feeding. The Western Cape Province provided free commercial formula milk, for 6 months to

HIV-infected women whose initial choice was not to breastfeed. Formula feeding had a high uptake (>70%) with relatively low rates of breastfeeding, in the province. Two years later, in 2012, the Western Cape PMTCT program transitioned from formula feeding policy to providing HIV-infected women with lifelong cART and promoting breastfeeding. During the transitional period, HIV-infected women were counselled by primary healthcare nurses and trained lay counsellors to choose between exclusive breastfeeding and formula feeding. The guidelines were further updated in March 2013 recommending a standardised triple-cART to treat HIV-infected pregnant and breastfeeding women, regardless of CD4 count, with continuation of cART after breastfeeding for women with CD4 counts less than 350 (84).

Knowledge gaps
Exclusive breastfeeding is the reference feeding methods against which all other infant feeding methods must be measured with regard to infant growth and morbidity. However, neither exclusive breastfeeding nor exclusive formula feeding is the cultural norm in most African settings (85, 86). For example, majority (>80%) of South African women initiate breastfeeding but only 26% of the women report exclusive breastfeeding in the first 6 months (87). Many factors, including practical, economic, social, psychological and cultural challenges have been associated with suboptimal infant feeding practises (88, 89). Poor counselling has been linked to these challenges (90). In addition, the risk of HIV transmission through breast milk has made infant feeding practices complex in the context of HIV (91).

Feeding modality is central to achieving optimal growth and health of infants born to an HIV-infected woman, but of concern is the emerging evidence showing that HIV-exposure may also influence health outcomes of HIV-exposed uninfected infants (92, 93). There are many possible ways that could increase the risk for poor health outcomes of an HIV-exposed uninfected infant. The HIV-exposed foetus is exposed to maternal HIV and to antiretroviral drugs in-utero (94). Often HIV-exposed infants are exposed to other infectious agents, including Mycobacterium tuberculosis, than HIV-unexposed infants and all these contribute in varying degrees to poorer health outcomes (95-97). HIV-exposed infants including uninfected infants are exposed to long courses of ARV drugs, and the effects of the drugs on HIV-exposed uninfected infants' growth are not well established (93).

Two studies conducted in Africa comparing HIV-exposed uninfected to HIV-unexposed uninfected infants for all-cause mortality or infectious morbidity (98,99), found increased morbidity in HIV-exposed uninfected infants, however, other studies conducted prior to ART era concluded that HIV-exposed uninfected infants were no different from HIV-unexposed uninfected infants for morbidity and mortality (100,101). However, most of the evidence from

the pre-ART era, suggests that HIV-exposed uninfected infants experience greater morbidity and mortality than HIV-unexposed uninfected infants.

Many PMTCT programs in high prevalent settings including the Western Cape, rapidly adopted Option B+, where until recently there was high uptake of formula feeding and relatively low rates of breastfeeding by HIV-infected women. The feeding guidelines are informed primarily by evidence from tightly controlled studies. These studies evaluate the effects of alternative infant feeding options on important clinical outcomes under highly controlled conditions. The limitation of such studies is that the findings may not reflect what happens in real life settings, where the same level of control is unlikely (10).

Despite the current recommendations to provide lifelong cART and promote breastfeeding among HIV-infected women, there are limited data on growth and morbidity of HIV-exposed uninfected infants in normal practice settings. Furthermore, the Western Cape PMTCT program provided free infant formula for HIV-exposed infants until the age of 6 months. Yet there is no published data on health outcome of these infants after free formula supply was stopped.

Moreover, the implementation of HIV infant feeding guidelines has been a challenge in many low-resourced settings (12). While the Option B+ strategy is a sound medical and public health approach, the shift in formula policy by Western Cape PMTCT program may not have given much consideration to social, and contextual issues affecting HIV-infected women's infant feeding practices (12,102).

Conceptual framework
We found that some factors have a substantial influence on infant feeding and related health outcomes in the context of HIV:

- Infant feeding practices
- Socio-demographic and cultural backgrounds
- social and contextual factors influencing HIV-infected women's infant feeding perceptions and practices
- Effort invested in controlling infant feeding guideline adherence of HIV-infected women and healthcare providers (context)

The framework that emerged from the theoretical overview presented in this chapter is that infant feeding and its influence on health outcomes is complex and consists of a number of factors that are both related and interdependent (see Figure 2.1). The model portrays four variables that reflect their interdependency within the infant feeding context. Each variable

contribute in part to the interactional relationships, and the interaction of the variables overall, helps to explain the influence of infant feeding on infant health outcomes.
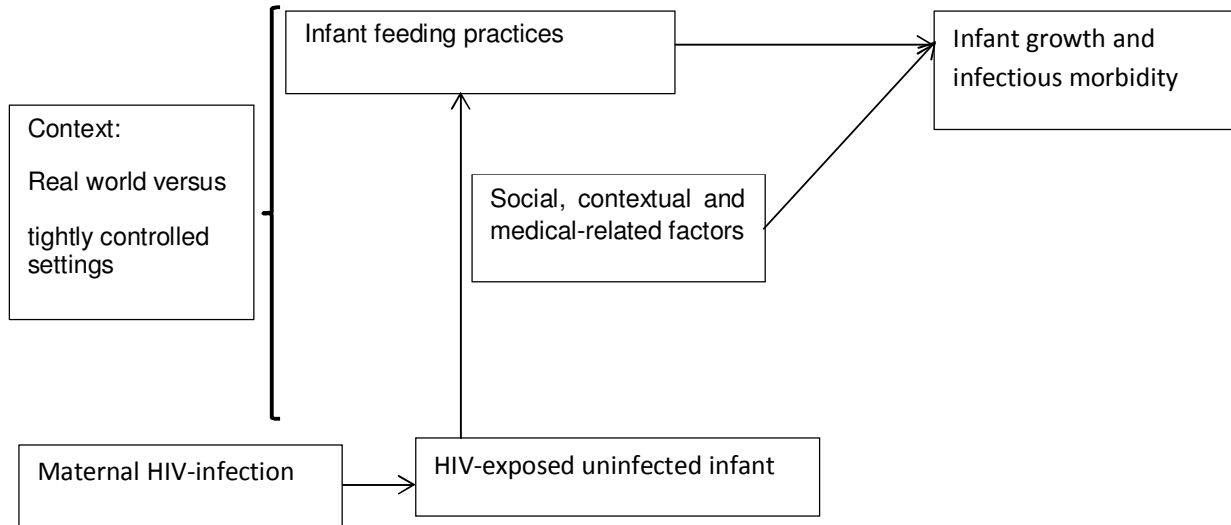
Figure 2.1 Theoretical overview of the influence of infant feeding on HIV-exposed uninfected infants' health outcomes

We performed a longitudinal cohort study on the effects of predominant breastfeeding and predominant formula feeding on infant growth and infection-related hospitalizations, among HIV-exposed uninfected infants in primary healthcare settings. We also explored HIV-infected women's experiences and perceptions on breastfeeding and formula feeding during a time the Western Cape PMTCT program was transitioning to providing all HIV-infected women with lifelong cART and promoting breastfeeding.

Chapter 3

Part A: Mother Infant Health Cohort Study

Introduction

The two studies were planned in phases. The aim of the qualitative study was briefly stated in the longitudinal cohort study main protocol. At a later stage, during evaluation of the longitudinal cohort study, the qualitative study was added as an amendment to the main protocol (approved by ethics committee). The longitudinal cohort study addressed the questions: i) whether breastfeeding practices of HIV-infected and uninfected women were different and ii) whether predominant breastfeeding compared to predominant formula feeding improves growth and reduces infection-related hospitalizations of HIV-exposed uninfected infants in infants from the same community setting.

I developed the research questions for the two studies and contributed in conception and design of both the cohort and the qualitative studies.

Aims

The study aim was to determine the effect of feeding practices on infant growth and infectious morbidity in a real world setting of implementation.

Primary objectives

1. Describe HIV-infected women's infant feeding practices in a real setting of implementation

2. Compare infant feeding practices of HIV-infected and HIV-uninfected (included in the Mother-Infant Health study) women, whose initial choice was to breastfeed

3. To determine the effect of predominant breastfeeding and predominant formula feeding in improving growth (weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ) z-scores) of HIV-exposed uninfected infants in primary healthcare clinics, over 12 months.

4. To determine the effect of predominant breastfeeding and predominant formula feeding on weight velocity Z-scores (WVZ), length velocity Z-scores (LVZ) of HIV-exposed uninfected infants in primary healthcare settings, during the first 6 months

The null hypotheses were that the growth of HIV-exposed uninfected infants who were predominantly breastfed was similar to that of predominantly formula fed infants.

5. To determine the effectiveness of predominant breastfeeding and predominant formula feeding in reducing the odds of infection-related hospitalizations of HIV-exposed uninfected infants in primary healthcare clinics, over 12 months.

The null hypothesis was that HIV-exposed uninfected infants who were predominantly breastfed had similar infection-related hospitalizations to predominantly formula fed infants.

Methods and Design

Study design

We established a longitudinal cohort study of HIV-infected women and their exposed infants. Neither breastfeeding women nor their infants were matched with women and infants in the formula feeding group in any way. However, possible confounders such as socio-demographic and clinical characteristics were assessed and later tested to see if there were any significant differences between the groups (see Figure 3.1 Study design sketch). This was part of a larger study, the Mother-Infant Health Study that was comparing infection-related hospitalizations among HIV-exposed uninfected (n = 94) and HIV-unexposed infants (n = 82). The main objective of the Mother Infant Health Study (MIHS) was the effect of HIV exposure on infection-related morbidity in the first 6 months of life (primary objective) and at 12 months (secondary objective). Infant feeding was a covariate, whereas, this study closely evaluated infant feeding practices for which the MIHS had no data. HIV-uninfected women were the comparative group in the MIHS and their breast feeding patterns were included in our study to contrast with those of the HIV-infected women.

HIV-infected women and their infants were selected according to the eligibility

A target sample size of at least n=188 HIV-infected women and their HIV-exposed uninfected infants on breastfeeding and formula feeding

Enrolled

Excluded: Inclusion criteria not met (see Table 3.1)

Exposure groups (mothers self-selected infant feeding practice)

HIV-infected women and their HIV-exposed infants: Breastfeeding (n = 94)

HIV-infected women and their HIV-exposed infants: Formula feeding (n = 94)

Baseline assessment:

- Socio-demographic data
- Clinical data (ART)

Baseline assessment:

- Socio-demographic data
- Clinical data (ART)

Follow-up (2week; 2, 4, 6, 9, 12 month of age):

- Health assessment
- Infant feeding practices
- ART adherence
- Weight, length measurements
- Hospitalization for illnesses

Follow-up (2week; 2, 4, 6, 9, 12 month of age):

- Health assessment
- Infant feeding practices
- ART adherence
- Weight, length measurements
- Hospitalization for illnesses
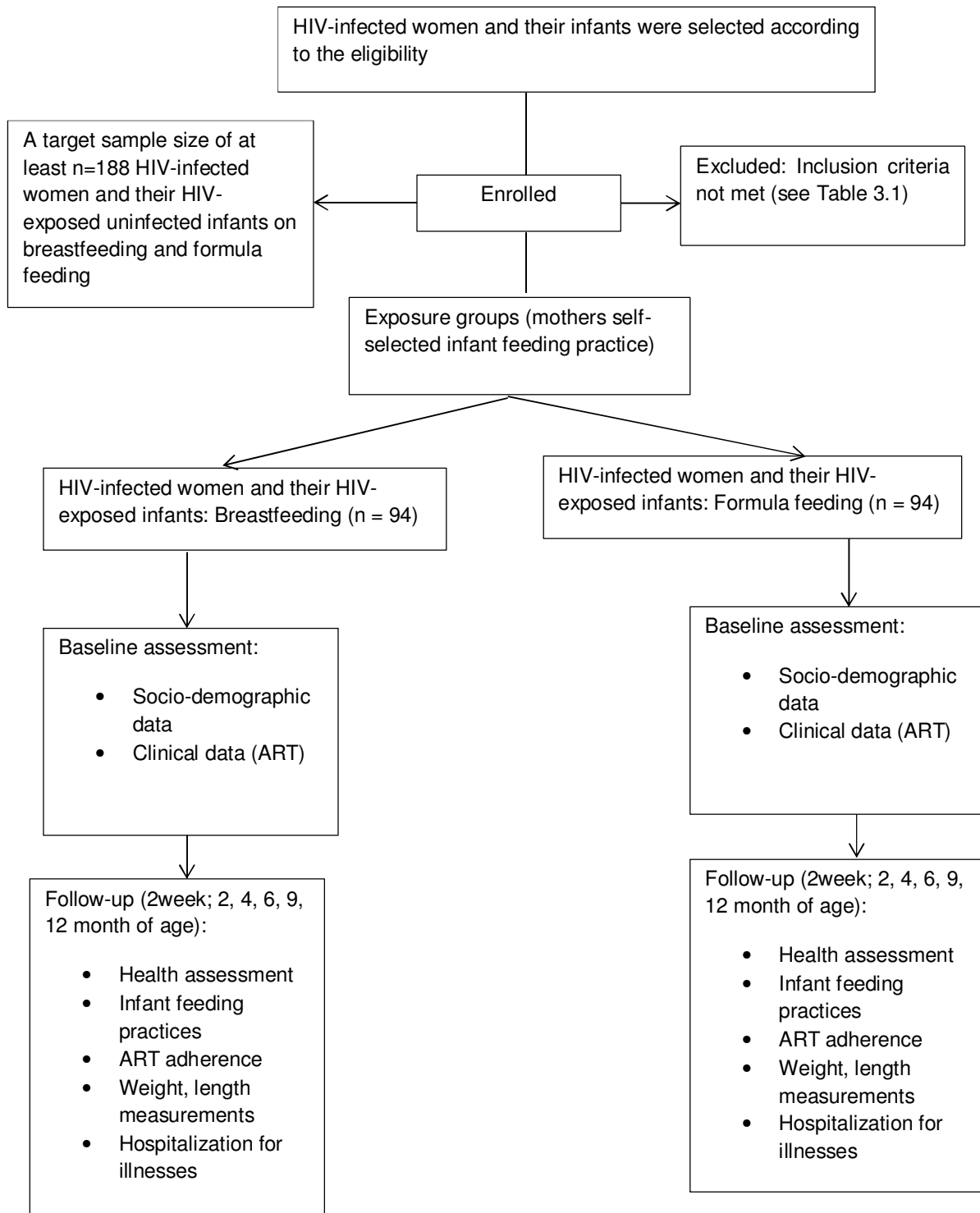
Figure 3.1 Study design: Exposure groups according to intended infant feeding option at enrolment

Participants and setting

Women from four suburbs (from Kraaifontein midwife obstetric unit drainage area) with comparable low socioeconomic status, who gave birth between July 2012 and December 2013 at Kraaifontein Midwife Obstetric Unit, a primary healthcare unit in an underserved

30

community in Cape Town, were invited to participate in the study. Women could participate in the study if they were at least 16 years of age and delivered at the obstetric unit. We evaluated HIV-uninfected women and women who were HIV-infected, had been on AZT for ≥ 2 weeks or on cART for ≥ 6 weeks before delivery; women who were pregnant with more than 1 infant were excluded. Infants of HIV-infected women were enrolled if they had a birth weight of at least 2000g and a gestational age of 36 weeks or more (see Table 3.1 Study eligibility criteria).

Three quarters of women delivering at the unit are black Africans with the remainder being coloured. At the beginning of study recruitment (15 July 2012), about 75% of HIV-infected women preferred formula feeding as their infant feeding practice, with 25% choosing breastfeeding with ARV treatment (personal communication – Dr Amy Slogrove, 18 May 2011).

Primary healthcare nurses screen pregnant women for HIV infection from 14 weeks of gestation through voluntary HIV counselling and testing services offered to all women seeking antenatal care at the healthcare facility. HIV prevalence was approximately 15% among women attending antenatal care in the district (21). Nurses ensure the following: PMTCT program entry for HIV-infected women, continuity of prophylactic and ART, and initiation of their neonates with antiretroviral prophylaxis. During the study, HIV-infected women were counselled to exclusively breast- or formula feed their infants for the first 6 months of life (83). Primary healthcare nurses provide ongoing post-partum care that includes supporting women on their infant feeding practices. HIV-exposed infants receive cotrimoxazole preventive therapy from six weeks after birth until HIV infection is excluded and breastfeeding has stopped, to reduce the risk of Pneumocystis jirovecii pneumonia related-death (9).

Participants were provided R100 (~US$10) at each follow-up visit to compensate for their time, as well as transportation reimbursement.

The study inclusion and exclusion criteria is shown in Table 3.1 below

Table 3.1 Study eligibility criteria

Inclusion criteria	Exclusion criteria
o HIV-infected women who intended to formula feed for at least six months	o Infants born before arrival to the obstetric unit
	o Women who never attended antenatal clinical care
o HIV-infected women who intended to breastfeed with ART for about one year	
o HIV-uninfected women (in the main study) who intended to breastfeed	
o HIV-uninfected women (taking part in the Mother Infant Health Study) who intended to breastfeed	
o Women at least 16 years of age	o Women with unknown or indeterminate HIV status
o Infant with no evidence of clinically significant health conditions (cardiac, respiratory, hepatic, gastrointestinal, endocrine, renal, haematologic, neurologic, or allergy) requiring care as assessed by the healthcare provider i.e. infant was judged to be in good health and was discharged after delivery)	o HIV-infected women on AZT started < 2 weeks before giving birth
	o Infant with birth weight <2000g
o Willingness to participate in all follow-up study visits, all clinical examinations and agreement for venepuncture for laboratory blood tests of their babies	o HIV-infected women on cART < 6 weeks before giving birth
o Women giving birth at Kraaifontein midwife obstetric unit	o Pregnant women with >1 infant
o Women from low income suburbs of Kraainfotein MOU drainage area	
	o Gestational age of < 36 weeks at birth
	o Women who required intensive care or admitted to a hospital for care
	o Sick new born hospitalized or referred for further management
	o Women who could not attend follow-up

study visits

○ Women enrolled in an HIV-vaccine study

Data collection and study follow-up

Data collection tools included a baseline questionnaire at enrolment, and follow-up questionnaires used at 2 week, 2, 4, 6, 9 and 12 months post-delivery). Follow-up data collection tools included; biological specimen case report forms, hospitalization case report forms, mother-infant health assessment and infant feeding questionnaires.

Enrolled women signed the consent to participate in the study and later follow-up. Consent was obtained in woman's local language. All women received a study information sheet that included details of; study aims, study procedures, and potential benefits and risks of participating in the study, decisions to withdraw from the study at any time without any change in care, study funding sources, and institutional affiliations of investigators.

Mother-infant pairs were followed-up at KID-CRU, in Tygerberg Academic Hospital. Research nurses took biological specimens and anthropometric measurements. Infant feeding questionnaires were completed by research counsellors. A study physician physically examined the infants and completed the mother-infant health assessment questionnaire at each study visit. Infants with health problems were referred either to Tygerberg Children's Hospital or to their local clinics for medical management, depending on the severity of the illness.

Questionnaires were administered in English, Xhosa or Afrikaans. In instances where study participants could speak only one local language, and the research staff could not speak the participant's language, one of the research team would translates questions directly.

The week before each study appointment, women were reminded telephonically about their scheduled study visits. Participants were provided with transport at follow-up visits. Follow-up data collection was completed on 5 December 2014.

Participant Retention

The following strategies were used to maintain adequate follow-up; contact details of participants and their next of kin were updated at each follow-up visit, telephone calls to those who missed study visits followed by home visits, free doctor consultations and physical examination of the child, telephone reminders, research team considered participants' working schedules when setting study appointments, free transports to and from research

sites, and ensured referral to specialised clinics when a condition requiring special care was identified.

Data sources and methods of measurement

Explanatory variables
Baseline maternal demographic, socioeconomic characteristics and clinical data were obtained by data abstraction from maternity case records and by interviewing the woman and these included: maternal age, marital status, highest level of education attained, birth history, HIV-infection status.

Antiretroviral treatment was given to the woman or the infant, depending on women's clinical indications. Participants collected their ART and infant formula milk from their local clinics. During follow-up visits we assessed infant immunization history, and women's adherence to cART. The immunization history was abstracted from road to health booklets. Self-reported adherence to ART or prophylaxis was assessed using a Likert scale assessing levels of adherence (from very poor to excellent) in the previous month, and this was based on a tool by Chaiyachati et al., 2012 (103).

Exposure variables
Infant feeding practice was treated as a time changing exposure variable and was therefore determined at enrolment and at each follow-up visit. The two exposure groups comprised of: predominantly breastfed and predominantly formula fed HIV-exposed uninfected infants. The study was conducted when the Western Cape PMTCT program was transitioning from formula feeding policy to providing all HIV-infected women with lifelong cART and promoting breastfeeding. HIV-infected women had a choice between exclusive breastfeeding and subsidized formula feeding during this transitional period. Free formula milk for 6 months was available to all HIV-infected women when the PMTCT program supported formula-rather than breast-feeding and during the transitional period (2002 – 2013). The mother decided on feeding practice during her interactions with the public program. The researcher accepted the mother's choice and recruited into the appropriate feeding group and supported mother's adherence to her infant feeding practice.

At each follow-up visit, research staff administered an infant feeding questionnaire. I developed the questionnaire based on a WHO standardized instrument (104), which inquired about feeding practices during the previous 24 hours and during the prior week. One week is suggested as the maximum recall period to obtain reasonably accurate data on infant feeding practices. The dynamics of infant feeding are acknowledged to be complex and difficult to capture, feeding practices may have changed between follow-up visits (104) and this is acknowledged as a limitation of the study.

HIV testing of infants was done at 2 weeks and 6 months using a DNA polymerase-chain-reaction assay (PCR) and at 12 months using an enzyme-linked immunosorbent assay (ELISA). A DNA PCR confirmatory test was performed on infants who had reactive ELISA test results. All testing was performed at the National Health Laboratory Services at Tygerberg Hospital.

Infant feeding practices were defined according to WHO: (104)

1. Predominant breastfeeding: Infant receiving mainly breast milk as well as other liquid or solid foods, but not formula milk.

2. Predominant formula feeding: Infant receiving mainly formula milk and other liquid or solid based foods, but not breast milk.

3. Exclusive breastfeeding from birth up to 6 months of age: Feeding practices where an infant received only breast milk and no other liquids or solids, including water, but may have received drops or syrups consisting of vitamins, mineral supplements, or medicines that were considered necessary and essential for the child.

4. Exclusive formula feeding from birth up to 6 months of age: Feeding practices where an infant received only infant commercial formula and no other liquid or solid, including water, but may have received drops or syrups consisting of vitamins, mineral supplements, or medicines that were considered necessary and essential for the child.

5. Mixed feeding: Breastfeeding as well as giving other milks (including commercial formula or home–prepared milk) and other liquid and solid based foods.

Outcomes variables
The outcomes were measured at each study visit over the 12 months period.

Infant growth
Infant weight was measured using a digital scale and length measurements were taken while infants were lying down, using a length board. WAZ, LAZ, and WLZ were estimated using WHO 2006 growth standard (105).

Infection-related hospitalization
Mothers self-reported infant hospitalizations related to any illnesses, during interviews with the study physician. In addition, we searched the national health information service system (Clinicom) to identify any hospitalizations that occurred among enrolled infants. With another investigator I abstracted information on reason for admission from the medical records. A study hospitalization chart abstraction guide (see Appendix 2) was used and the abstracted information was recorded on de-identified standardized case report forms.

Two paediatricians who were unaware of the feeding mode of the infants reviewed the abstracted information and independently classified the hospitalizations using an infection classification tool. The infection classification tool, Paediatric Infectious Event Tool for Research (see Appendix 3) was designed and validated based on published guidelines (106-110).

Data management

Data were transcribed from the paper format into an online electronic database (OpenClinica). The data were checked to ensure that entered values were acceptable, required fields were entered, and items were consistent with other related items in the database. I verified the source documents for any discrepant entries that were generated in the validation reports. I sent queries electronically to the data manager to address the discrepant entries and this continued until the queries were resolved. A record of the database update was kept, identifying information about the person who made the changes, date, changed values and comments. R program (version 3.1.2) was used to develop the program for the validation checks.

Sample size and power justification

Assuming mean WAZ-scores (standard deviations) (SD) of 0.17 (0.95) and 0.61 (1.17) in predominantly formula fed and predominantly breastfed infants, respectively, 188 HIV-exposed uninfected infants were required, to reject the null hypothesis that WAZ- scores at 6 months of age, were similar between the 2 groups, with probability (power) of 0.80, with half in the breastfeeding group and the other half in the formula feeding group. The mean (SD) WAZ-scores were based on two South African studies (111,112).

Statistical Methods

Only HIV-exposed infants who remained HIV-1 negative by PCR or ELISA test and had at least one follow-up visit were included in analysis.

T-test was used to compare the distribution of baseline continuous variables between breastfeeding and formula feeding groups. Categorical variables were compared between the two feeding groups using Pearson's chi-square or Fisher's exact test.

The 2006 WHO growth standards were used to calculate WAZ, LAZ and WLZ at each study visit (105). Hypotheses tests were 2-tailed with level of significance set at $p < 0.05$. The 95% CIs were used to estimate parameters. Stata (StataCorp. 13. Stata Statistical Software: Release13. College Station, TX: StataCorp LP) was used for analyses. A summary of methods of analysis for each outcome variable is provided in Table 3.2 below. I performed the statistical analyses with help of a statistical mentor, Prof Rhoderick Machekano.

Table 3.2: Variables, Measures and Methods of Analysis

Variable/Outcome	Hypothesis	Outcome Measure	Methods of Analysis
a) Infant growth at each study visit	Breastfeeding improves growth	WAZ-scores [continuous] LAZ-scores [continuous] WLZ-scores [continuous]	t-test
b) Infant growth velocity (increments per age interval)	Breastfeeding improves growth velocity	WVZ [continuous] LVZ [continuous]	t-test, multiple linear regression
c) Infection-related hospitalizations over 12 months	Breastfeeding reduces infection-related hospitalizations	Infection-related hospitalization [binary]	Mixed effects logistic regression

Ethical aspects

The study was approved by the Human Research Ethics Committee of Stellenbosch University (Ref: S12/03/065). Permission to conduct the study was obtained from the Western Cape Department of Health (Ref: RP 22/2012). The study was conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research. All participants provided a written informed consent for study participation. Note: We did not get assent for women below the age of 18 years but the Human Research Ethics Committee gave permission to consent women from age 16 years and above although there was one woman below 18 years.

All study participants, irrespective of their feeding practice, received health services and treatment according to the respective provincial guidelines applicable in the sector at the time the study was executed, and no deviation from existing guidelines was caused by taking part in this study.

Potential risks for this study included the possibility of loss of confidentiality concerning HIV status of the mother and that of the infant and other identifiable data. Standardized procedures were maintained by the research term to ensure participants' confidentiality.

Information received from participants was not disclosed with a third party. This being an observational study; there were no physical risks involved in the study. Participants were insured by Stellenbosch University's research policy in the event of physical injury as a direct result of study participation.

All study questionnaires in paper format are stored in safe locked cabinets at KID-CRU, Tygerberg Hospital. The electronic database is secure and only accessible to the research team through a user name and password. Statistical analyses of the study results were presented in aggregate format in technical reports and conference proceedings.

Part B: Qualitative study design

HIV-infected women's perception and reaction to infant feeding practices

Introduction

The longitudinal cohort study assessed the effect of predominant breastfeeding and formula feeding on improving infant growth and reducing the risks of infection-related hospitalizations. Often, however, it is insufficient to have only information about the effect of an infant feeding option on clinical outcomes to inform both those affected or healthcare decision makers. The qualitative analysis gives a rigorous description of the subjective experiences HIV-infected women had with the recommended feeding options. In combination with the longitudinal cohort study, the qualitative analysis provides contextual and social factors affecting women's feeding practices that may relate directly to its uptake in a real world setting. The aim of the qualitative sub-study was to explore HIV-infected women's experiences and perceptions on breastfeeding and formula feeding during a time when the Western Cape PMTCT program was transitioning to providing all women with lifelong cART and promoting breastfeeding.

Study methods

Participants

A sub-set of HIV-infected women participating in the longitudinal cohort study was invited to participate in a breastfeeding and formula feeding focus group discussion and individual qualitative interviews. HIV-infected women who were followed-up for at least 6 months post-delivery in the longitudinal cohort were eligible to participate in the qualitative study. Study participation was not restricted by women's language. The women were contacted by telephone and invited to participate. The qualitative study was conducted between November-December, 2013. Focus group discussions were conducted separately by feeding modality (i.e. breastfeeding or formula feeding) and took about four hours to complete. Individual interviews were each approximately 1 hour in length. Focus group discussions and individual interviews were conducted at KID-CRU, in Tygerberg Academic Hospital. All discussions and interviews were audio-recorded.

A total of 38 (breastfeeding (n = 15), formula feeding (n = 23)) women were invited to participate in the qualitative study, of these 8 refused to participate. Seven breastfeeding and eight formula feeding women participated in focus group discussions and twenty-three participated in the individual interviews (eleven of whom were breastfeeding). Among those

who participated in the individual interviews, three formula feeding and five breastfeeding women had participated in the focus group discussions.

The sample of eight formula feeding and seven breastfeeding women who participated in focus group discussions was fairly adequate. Northcutt and McCoy, authors of the Interactive Qualitative Analysis methods used for the qualitative study suggest that focus group representation should include 12 to 20 participants (113) . The authors also comment that small focus groups are not a serious problem during identification of factors describing their experiences with a certain phenomenon under study but may only skew data when looking at relationships between the factors. In our study 23 women participated in the individual qualitative interviews where we looked at the relationships between the factors affecting their infant feeding experiences.

Study design
An Interactive Qualitative Analysis method was used, where HIV-infected women close to a phenomenon under study (infant feeding experiences) described, labelled their experiences, and articulated perceived relationships among their experiences to produce a system influence diagram (mental model) representing how the women understood their infant feeding experiences (113). The method uses Systems Theory (114) to conceptualize a phenomenon as comprising a system of factors and relationships among the factors. The factors in IQA research represent categories of meaning from a group sharing a common experience on an issue. To understand a system, the factors of the system and relationships among the factors are identified and described. Focus group discussions are used to identify the factors. The focus group participants are asked to silently reflect and write their experience, thoughts, beliefs and feelings on the issue under study (113). Relationships reflect participants' perceptions of the association among the factors.

Focus group discussions: Identification of system 'factors'
To identify the factors associated with infant feeding practices, the focus group participants were given an opportunity to reflect on their infant feeding experiences and then express their thoughts and emotions involved. This assisted focus group participants in organising their thoughts into a manageable number of sets of textual references that have an underlying common meaning or theme. Participants documented their infant feeding experiences on note cards, one experience per card. Once completed, the cards were taped on a wall. The facilitator read aloud the contents of each card and guided participants in clarifying their understanding of the responses on each card to eliminate any ambiguity associated with the meanings of the words or phrases. The group had to reach consensus on the meaning of each card's contents. The purpose was to arrive at a socially constructed, shared meaning of the contents of each card among focus group participants. Assisted by

facilitators, participants reviewed all the cards on the wall and clustered them into factors or common themes. When the majority of the cards were clustered, the facilitators helped participants to identify an appropriate label for each cluster. Any cards that were miscategorised were sorted into appropriate category.

Open-ended individual qualitative interviews
Individual interviews for breastfeeding women were guided by factors that emerged from the breastfeeding focus group discussion, and similarly for formula feeding women. The facilitator shared the focus group's description of each factor with the individual woman and then engaged in a dialogue to explore the personal meaning, and life history experiences of the woman on the factor.

During the individual interviews, participants were asked to describe the relationship between the factors identified in the focus group discussions. This was facilitated by asking the participant to speak about the three possible types of relationships between each pair of 'factors' as follows: A influences B (A→B), B influences A (A←B), or no clear relationship (A<>B). In the interviews, this exercise was presented as follows: "Look at A and B, as you think about what you have said about these factors, do you see a direct connection between these two or some sort of influence between these two? Explain why you believe so or would you give an example from your own experiences, opinion, values or feelings with the relationship between A and B". Exploring participants' perceptions of relationships between 'factors' enabled a deeper understanding of how they experienced infant feeding.

Factor description and analysis
Quotes gathered from index cards that were generated by focus group participants, transcripts of the focus group discussions and from the individual interview were used to develop composite descriptions to illustrate the range of meaning for each factor. This was supplemented by the individual interviews resulting in rich descriptions for each factor.

A summary description of the factors describing HIV-infected women's infant feeding experiences was generated separately for women who breast- and formula fed. The 'System Influence Diagrams' (SIDs) (113) served as graphical representations of relationships among factors affecting women's experiences of infant feeding. The SIDs served as a basis for further thematic analysis of women's experiences relative to understanding their decision between breast and formula feeding.

Ethical aspects
A verbal consent was obtained from all participants participating in the qualitative study. Participants were made aware that; they were free to express their thoughts without penalty, their identity was protected, and there were no reprisals due to their participation. The

qualitative study and verbal consent for participation in the qualitative study was approved by Stellenbosch University, Human Research ethics committee as an amendment of the main protocol.

Chapter 4

Infant feeding practices and effects on infant growth and morbidity in PMTCT programs transitioning to "Option B+" in Western Cape, South Africa

Abstract

Introduction
Despite the current recommendations for HIV-infected women to breastfeed with combination antiretroviral treatment, there are limited data on growth and morbidity of HIV-exposed infants in normal practice settings. The objectives of this study were to describe infant feeding practices of HIV-infected women and compare to those of HIV-uninfected women and to determine the effect of predominant breastfeeding and predominant formula feeding on growth and morbidity of HIV-exposed infants, over a 12 months period.

Methods
We established a longitudinal cohort study of HIV-infected women and their infants, between July 2012 and December 2014. HIV-infected women had a choice between exclusive breastfeeding and subsidized formula feeding. The mother decided on feeding practice during her interactions with the public PMTCT program. Free formula milk for 6 months was available to all HIV-infected women whose initial choice was not to breastfeed. The cumulative probabilities of remaining predominantly breastfeeding were compared between HIV-infected and HIV-uninfected women using Kaplan-Meier estimation methods and log-rank test. Infant growth rates were estimated and compared between feeding groups using linear mixed effects models. Infection-related hospitalizations were modelled as a binary outcome in a mixed effects logistic regression model.

Results
One hundred twenty-one HIV-exposed uninfected infants were included in the analysis. Of these, 50 (41%) were in the breastfeeding group and 71 (59%) were in the formula feeding group. The proportion of women who remained predominantly breastfeeding during follow-up was slightly lower among HIV-infected women than HIV-uninfected women (p = 0.0005). By about 4 months half of the HIV-infected women had switched to predominant formula feeding. After adjusting for women's educational level and cART status, mean weight velocity z-scores (95% CI) of predominantly breastfed infants in the 2 to 4 age interval was -0.70 (-1.31 to -0.09) lower than the mean of predominantly formula fed infants, p =0.024. Attained WAZ, LAZ and WLZ were similar between feeding groups at each study visit. There were 27 infection-related hospitalizations, 5 of these occurred among predominantly breastfed and 22 among predominantly formula fed infants. After adjusting for woman's

educational level, cART status, and infant age, the odds of infection-related hospitalizations among predominantly breastfed infants were 5% lower than of predominantly formula fed infants, odds ratio (OR) 0.95 (95% CI: 0.33 to 2.74).

Conclusion

Many women stop breastfeeding early, despite the recommendations favouring breastfeeding. Strategies to promote and sustain continued breastfeeding by women, to levels that would result in a significant impact on the health of their children are urgently needed. The strategies should be guided by women's understanding of HIV transmission through breast milk, quality of counselling, stigma and constraints of economic realities affecting women's feeding practices.

Introduction

Since the discovery that HIV can be transmitted through breast milk more than 30 years ago (46-48), information has been accumulating to guide infant feeding guidelines for HIV-infected women in low-resourced settings.

In 2001, the WHO recommended formula feeding for HIV-infected women in low-resourced settings based on experiences from high-income countries (59). The drawbacks of the guidelines were that most HIV-infected women in low-resourced settings could not afford formula milk and formula feeding was also associated with increased risk of death from malnutrition and serious illnesses such as diarrhoea, respiratory and middle ear infections (115). The protective role of breastfeeding against infant morbidity, mortality and poor growth, especially in low-resourced settings is well established (1,70). However, there was also a substantial risk of HIV transmission to the infants through breast milk (116). The guidelines were therefore revised to further minimise the risk of HIV transmission based on studies showing that cART or prophylaxis given either to the mother or infant reduces the risk of HIV infection through breast milk (5,77). The WHO guidelines of 2010 and 2013 took into consideration provision of cART to the woman either for a recommended period or for life, respectively. The current guideline (WHO 2013), recommends triple-cART, irrespective of women's CD4 count, which has to be maintained at least for the duration of breastfeeding or as lifelong treatment, also called "Option B+" (9). Countries that have successfully implemented these guidelines have reduced the numbers of HIV-infected children to <2%, resulting in a growing population of HIV-exposed uninfected infants. There is emerging evidence showing that HIV-exposure may also influence health outcomes of HIV-exposed uninfected infants (92, 93). There are many possible ways that could increase the risk for poor health outcomes of an HIV-exposed uninfected infant. The HIV-exposed foetus is exposed to maternal HIV and to antiretroviral drugs in-utero (94). Often HIV-exposed infants are exposed to other infectious agents, including Mycobacterium tuberculosis, than HIV-unexposed infants and all these contribute in varying degrees to poorer health outcomes (95-97). HIV-exposed infants including uninfected infants are exposed to long courses of ARV drugs, and the effects of the drugs on HIV-exposed uninfected infants' growth are not well established (93).

The implementation of these guidelines has been a challenge in many low-resourced settings (12). Many factors, including practical, economic, social, psychological and cultural challenges have been associated with suboptimal infant feeding practises (88, 89). Poor counselling has been linked to these challenges (90). In addition, the risk of HIV transmission through breast milk has made infant feeding practices complex in the context of HIV (91).

The South African national PMTCT program adopted the WHO guidelines in 2010 (83). At the time, however, the South African national PMTCT guidelines promoted both exclusive breastfeeding and formula feeding. Healthcare authorities from the provinces supported different feeding options, with most choosing exclusive breastfeeding and a few supporting formula feeding. HIV-infected women in the Western Cape were provided free commercial formula milk, until the infant was 6 months old. Formula feeding had a high uptake (>70%) with relatively low rates of breastfeeding, in the province. Two years later, in 2012, the Western Cape PMTCT program transitioned from formula feeding to breastfeeding with cART. During the transitional period, women had an option to choose either exclusive breastfeeding or formula feeding. This unique transition scenario caused confusion for both healthcare providers who advised and for HIV-infected women who had to make a difficult choice.

The feeding guidelines for HIV-infected women in low-resourced settings are primarily informed by studies conducted under ideal conditions. Most of these studies put much effort on controlling guidelines adherence of investigators and participants. The limitation of such studies is that the findings may not reflect what happens in real world settings, where HIV-infected women are not closely monitored. Study findings from normal practice settings are likely to reflect what happens to a larger population of HIV-infected women and infants born to HIV-infected women, and are therefore likely to inform infant feeding policy and practice for HIV-infected women in low-resourced settings. Despite the current recommendations for providing lifelong cART and promoting breastfeeding among HIV-infected women, there are limited data on growth and morbidity of HIV-exposed uninfected infants in normal practice settings.

The primary objectives of this study were to: a) describe infant feeding practices of HIV-infected women, b) compare infant feeding practices of HIV-infected and HIV-uninfected (included in the Mother-Infant Health study) women, whose initial choice was to breastfeed, c) assess the effect of predominant breastfeeding and predominant formula feeding on attained growth, growth velocity and infection-related hospitalizations among HIV-exposed uninfected infants, over a 12 months period. The study was conducted during a time the Western Cape PMTCT program was transitioning to providing all women with lifelong cART and promoting breastfeeding.

Methods

Study design
We performed a longitudinal cohort study of HIV-infected women and their exposed infants over a 12 months period. This was part of a larger study, the Mother-Infant Health Study that

was comparing infection-related hospitalizations among HIV-exposed uninfected (n = 94) and HIV-unexposed infants (n = 82). The main objective of the Mother Infant Health Study was the effect of HIV exposure on infection-related morbidity in the first 6 months of life (primary objective) and at 12 months (secondary objective). Infant feeding was a covariate, whereas, this study closely evaluated infant feeding practices for which the Mother Infant Health Study had no data. HIV-uninfected women (n = 81) were the comparative group in the Mother Infant Health Study and their breast feeding patterns were included in our study to contrast with those of the HIV-infected women.

Study population and setting
Women from four suburbs (from Kraaifontein midwife obstetric unit drainage area) with comparable low socioeconomic status, who gave birth between July 2012 and December 2013 at Kraaifontein Midwife Obstetric Unit, a primary healthcare unit in an underserved community in Cape Town, were invited to participate in the study. Women could participate if they were at least 16 years of age and delivered at the obstetric unit. We evaluated HIV-infected women who had been on AZT for ≥ 2 weeks or on cART for ≥ 6 weeks before delivery; women who were pregnant with more than 1 infant were excluded. Infants of HIV-infected women were enrolled if they had a birth weight of at least 2000g and a gestational age of 36 weeks or more. Mother-infant pairs were followed for 12 months post-delivery at KID-CRU, Tygeberg Academic hospital in Cape Town. Final follow-up was completed in December 2014.

The protocol was approved by the Human Research Ethics Committee of Stellenbosch University. Participants were provided R100 (~US$10) at each follow-up visit to compensate for their time, as well as transportation reimbursement.

Study measurements and procedures
Baseline socio-demographic characteristics and clinical data were obtained by data abstraction from maternity case records and by interviewing the mother. Mother-infant pairs were followed-up at 2 weeks, 2, 4, 6, 9, and 12 months post-delivery. At each visit, research staff administered an infant feeding questionnaire based on a WHO standardized instrument (104), which inquired about feeding practices during the previous 24 hours and during the prior week. Infant weight and length were measured using a digital scale and a length board, respectively. Interviews were conducted in Xhosa, Afrikaans or English.

HIV testing of infants was done at 2 weeks and 6 months using a DNA polymerase-chain-reaction assay (PCR) and at 12 months using an enzyme-linked immunosorbent assay (ELISA). A DNA PCR confirmatory test was performed on infants with reactive ELISA test

results. All testing was performed at the National Health Laboratory Services at Tygerberg Hospital.

HIV-infected women had a choice between exclusive breastfeeding and subsidized formula feeding. The mother decided on feeding practice during her interactions with the public program. We accepted the mother's choice and recruited into the appropriate feeding group and supported mother's adherence to her infant feeding practice. Free formula milk for 6 months was available to all HIV-infected women whose initial choice was not to breastfeed. Antiretroviral treatment was given to the mother or the infant, depending on mother's clinical indications.

Clinical definitions

Predominant breastfeeding was defined as the infant receiving mainly breast milk as well as other liquid or solid foods, but not formula milk. Predominant formula feeding was defined as the infant receiving mainly formula milk and other liquid or solid based foods, but not breast milk (104). If infants were receiving both formula and breast milk during the same period, they were classified as receiving mixed feeding.

We searched the national health information service system (Clinicom) to identify any hospitalizations that occurred among enrolled infants. Two study investigators (including the principal investigator) abstracted information on the admissions. Two paediatricians who were unaware of the feeding mode of the infants reviewed the abstracted information and independently classified the hospitalizations as resulting from lower respiratory tract infections (including pneumonia, bronchiolitis, or tuberculosis), and diarrheal disease (acute, persistent, or dysenteric). Cases of discrepant classification were resolved by discussion.

Sample size and power justification

A total sample size of 188 HIV-exposed uninfected infants was required to reject the null hypothesis that WAZ- scores at 6 months of age, were similar between predominantly breastfed (n = 94) and predominantly formula fed (n = 94), with probability (power) of 0.80. This was derived from the mean WAZ-scores (SD) of 0.61 (1.17) and 0.17 (0.95) in predominantly breastfed and predominantly formula fed infants, respectively, observed in two South African studies, (111,112). All HIV-uninfected women in the Mother Infant Health Study (a convenience sample of n = 81) who met the eligibility criteria and had at least one follow-up visit were included in the analysis.

Statistical methods

Only HIV-exposed infants who remained HIV-1 negative by PCR or ELISA test and had at least one follow-up visit were included in analysis. Two infants who became HIV-infected

were censored at the time point they were confirmed HIV-positive. One was confirmed HIV-positive at 2 weeks after birth and was breastfeeding at baseline and the other was confirmed at 2 months and was formula feeding.

Infants who were lost to follow-up were censored at the last study visit. Similarly, infants who were neither breastfeeding nor formula feeding were included in analysis only at visits they were predominantly breastfeeding or formula feeding. Some women switched feeding modality between study visits; the infant was therefore assigned to the feeding practice group which the woman reported at that visit. A t-testing was used to compare the distribution of baseline continuous variables. Categorical variables were compared between the two feeding groups using Pearson's chi-square or Fisher's exact test. The cumulative probabilities of remaining predominantly breastfeeding were compared between HIV-infected and HIV-uninfected women using Kaplan-Meier estimation methods and log-rank test.

The 2006 World Health Organization growth standards were used to calculate attained WAZ, LAZ and WLZ at each study visit (105). Similarly a macro based on the 2009 WHO growth velocity standards was used to compute WVZ and LVZ (105) that represent growth rates over a period of time. Weight and length were standardized in reference to the normal growth rate in the specific age period. Mean WAZ, LAZ and WLZ were calculated for infants in each feeding group for each study visit. Mean WVZ and LVZ were estimated for three independent time intervals and were compared between feeding groups using t-test. The differences in mean WVZ and LVZ between predominantly breastfed and predominantly formula fed infants were estimated using multiple linear regression. Predominantly breastfed and formula fed infants were compared for the infectious-related hospitalizations in the first year of life, conditioned on mother's levels of education, cART status, and infant age in multivariate analysis. All socio-demographic, maternal and infant clinical characteristics were evaluated for possible confounding in univariate analyses. However, as this was a small study, which limited the number of variables to include in the multivariate analyses, priority was given to controlling for variables found in the literature to be important in influencing infant growth and infectious morbidity (117,118). The number of infection-related hospitalizations events further limited the number of covariates to include in the model. The response (infection-related hospitalizations) was binary valued (yes or no) at each follow-up visit. A generalized linear mixed effects logistic regression model was performed, assuming an unstructured covariance structure and allowing for within-child clustering. Infants who were hospitalized and had no information on their feeding practice at the time of hospitalization, because of a missed study visit were assigned the feeding group the mother reported adhering at the previous study visit.

Results

One hundred eighty-five HIV-exposed infants were enrolled, of these 121 were HIV uninfected and had at least one-follow-up visit and were included in the analysis; 50 (41%) were breastfeeding and 71 (59%) were formula feeding at baseline. Figure 4.1 displays the flow of participants and feeding practices at study visit.

121 HIV-exposed uninfected infants with at least one follow-up

50 intended to breastfeed

1 HIV-infected

2 weeks: 49 mother-infant pairs
41 breastfeeding
  7 formula feeding
  1 mixed feeding

8 LTFU*

2 months: 41 mother-infant pairs
32 breastfeeding
  9 formula feeding

2 LTFU

4 months: 39 mother-infant pairs
19 breastfeeding
19 formula feeding
  1 mixed feeding

2 LTFU, 1 missed the visit

6 months: 38 mother-infant pairs
10 breastfeeding
24 formula feeding
  4 mixed feeding

5 LTFU
2 missed the visit
1 neither breastfeeding nor formula feeding

9 months: 31 mother-infant pairs
  8 breastfeeding
22 formula feeding
  1 mixed feeding

5 LTFU
1 neither breastfeeding nor formula feeding

12 months: 28 mother-infant pairs
  4 breastfeeding
23 formula feeding
  1 mixed feeding

71 intended to formula feed

1 missed the visit

2 weeks: 67 mother-infant pairs
65 formula feeding
  1 breastfeeding
  1 mixed feeding

2 LTFU
1 HIV-infected
2 missed the visit

2 months: 64 mother-infant pairs
63 formula feeding
  1 mixed feeding

5 LTFU
5 missed the visit

4 months: 58 mother-infant pairs
57 formula feeding
  1 breastfeeding

6 LTFU
5 missed the visit

6 months: 52 mother-infant pairs
49 formula feeding
1 breastfeeding
2 mixed feeding

2 LTFU
4 missed the visit

9 months: 50 mother-infant pairs
49 formula feeding
  1 breastfeeding

8 LTFU
2 neither breastfeeding nor formula feeding

12 months: 45 mother-infant pairs
41 formula feeding
  1 breastfeeding
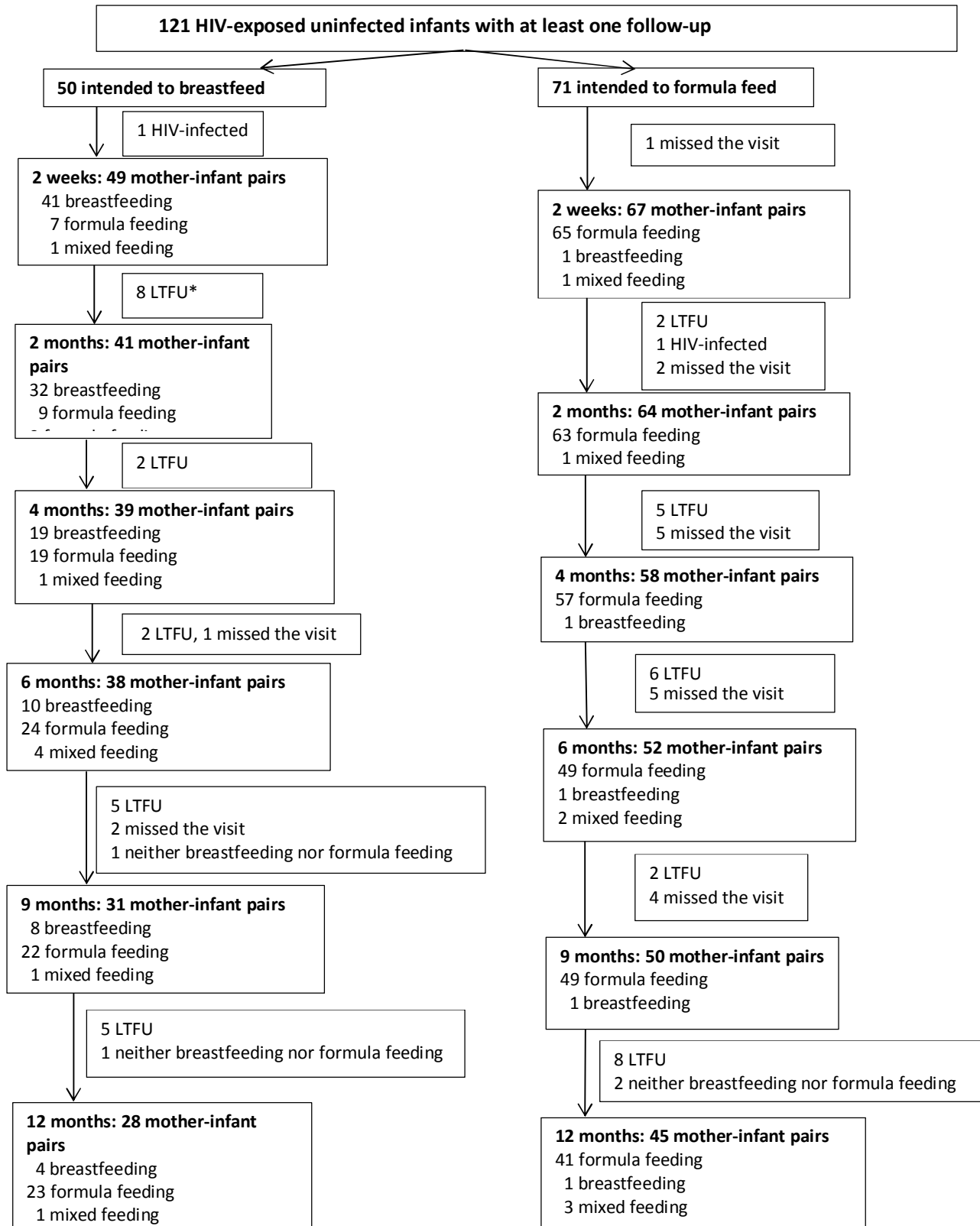 3 mixed feeding

Figure 4.1 Flow of study participants and feeding practices at study visit

*LTFU – Lost to follow-up

Baseline socio-demographic and clinical characteristics were similar between the groups, except that breastfeeding women tended to be less likely on cART than formula feeding women (44% versus 61%, $p = 0.07$) (Table 4.1). Almost all (98%) HIV-infected women were in WHO HIV stage 1 or 2 (data not shown). Mean infant birth weight was similar between the feeding groups. Almost all infants (99%) were started on NVP at birth.

Table 4.1 Characteristics of HIV-infected women, HIV-exposed uninfected infants and HIV-uninfected women, stratified by woman's feeding practice at enrolment

Characteristic	HIV-infected women			HIV-uninfected women
	Breastfeeding N=50 (41%)	Formula Feeding N=71 (59%)	p-value*	Breastfeeding N=81
Women				
Age, yrs (mean, ± SD)	27.86 ± 5.82	27.98 ± 6.32	0.91	26.13 ±5.25
Racial group			0.71	
Black African	44 (88)	64 (90)		73 (90)
Coloured	6 (12)	7 (10)		8 (10)
Marital status			0.80	
Never married	34 (68)	50 (70)		52 (64)
Married	14 (28)	17 (24)		28 (35)
Widowed/divorced	2 (4)	4 (6)		1 (1)
Educational level			1.00	
Primary	3 (8)	4 (6)		3 (4)
Secondary	47 (92)	67 (94)		78 (96)
†ART				------
On cART	22 (46)	43 (61)	0.07	
	N=26	N=27		
ART during pregnancy/delivery	26 (54)	27 (39)	0.80	
Smoking in pregnancy	N=49	N=68		
	6 (12)	9 (13)	0.87	3 (4)
Alcohol use in pregnancy	N=48	N=68		
	5 (10)	12 (18)	0.28	9 (11)
Piped water available	N=50	N=70		
	46 (92)	69 (99)	0.16	73 (90)
Flush toilet in home	N=50	N=70		
	49 (98)	69 (99)	1.00	80 (99)
Working refrigerator in home	N=50	N=70	0.39	
	35 (70)	53 (76)		63 (78)
Infants				
Female	27 (54)	34 (48)	0.51	45 (56)
Gestational age at delivery, wks, mean ± SD	38.4 ± 1.8	38.7 ± 1.8	0.35	39.2 ± 1.5
Birthweight (grams), mean ± SD	3090 ± 395	3133 ± 401	0.55	3236 ± 441
Birth length (cm), mean ± SD	49.1 ± 2.8	48.0 ± 4.3	0.11	49.7 ± 3.7

*p-values based on chi-square test or fishers exact test for categorical variables, and t-test for continuous variables; †Two HIV-infected women in the breastfeeding group and one women in the formula feeding group had missing information on ART

After 1 year of follow-up, 73 of 121 (60%) infants completed the study. The follow-up rate was 55% (28 of 51) in the breastfeeding group and 63% (45 of 71) in the formula feeding group. About 92% (12 of 13) and 87% (45 of 52) predominantly breastfeeding and formula feeding women reported their rate of adherence to cART as very good or excellent at 4 months post-delivery. At 6 months, 88% (74 of 84) had received required immunizations. Twelve HIV-infected women who mixed-fed at some point (giving their infants breast- and formula milk at the same time) was not an anticipated group and were not included in the initial objectives for evaluation. The women subsequently switched to either predominant breastfeeding or formula feeding, of these 5 were in the breastfeeding group at enrolment. Among HIV-infected women, the median (range) duration of exclusive breastfeeding was 1.9 (0.4 to 12) months and that of exclusive formula feeding was 4.0 (0.5 to 12) months, the median (range) duration of predominant breastfeeding was 2.0 (0.43 to 12.06) months and that of predominant formula feeding was 8.67 (0.46 to 12.75) months and the median (range) duration of mixed feeding was 4.04 (2.30 to 5.78) months. Among HIV-uninfected women, the median (range) duration of exclusive breastfeeding was 0.84 (0.46 to 6.5) months and the median (range) duration of predominant breastfeeding was 2.07 (0.46 to 12.42). Figure 4.2 displays the proportion of HIV- infected and uninfected women who remained predominantly breastfeeding during follow-up. The proportion of women who remained predominantly breastfeeding was slightly lower among HIV-infected women than HIV-uninfected women (p = 0.0005). These differences were seen from about 2 weeks, and persisted throughout follow-up. By about 4 months half of the HIV-infected breastfeeding women had switched to predominant formula feeding.
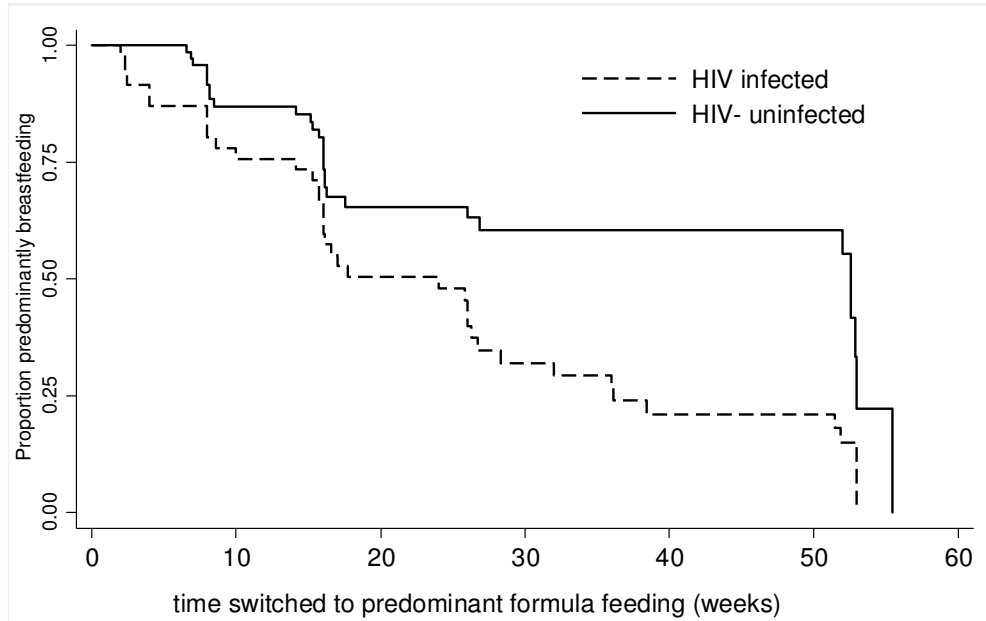
Figure 4.2 Proportion of HIV-infected and HIV-uninfected women who initially chose breastfeeding and remained predominantly breastfeeding during follow-up (logrank test *p* = 0.0005).

Infant growth

Figure 4.3 and Table 4.2 displays the average infant WAZ, LAZ, WLZ and corresponding 95% CI by feeding practice at study visit. Infants in all groups experienced exponential weight gain, with rapid increase in weight from birth to about 6 months. Attained growth was similar between feeding groups at each study visit. One predominantly formula fed infant had WLZ < -2 at 12 months.
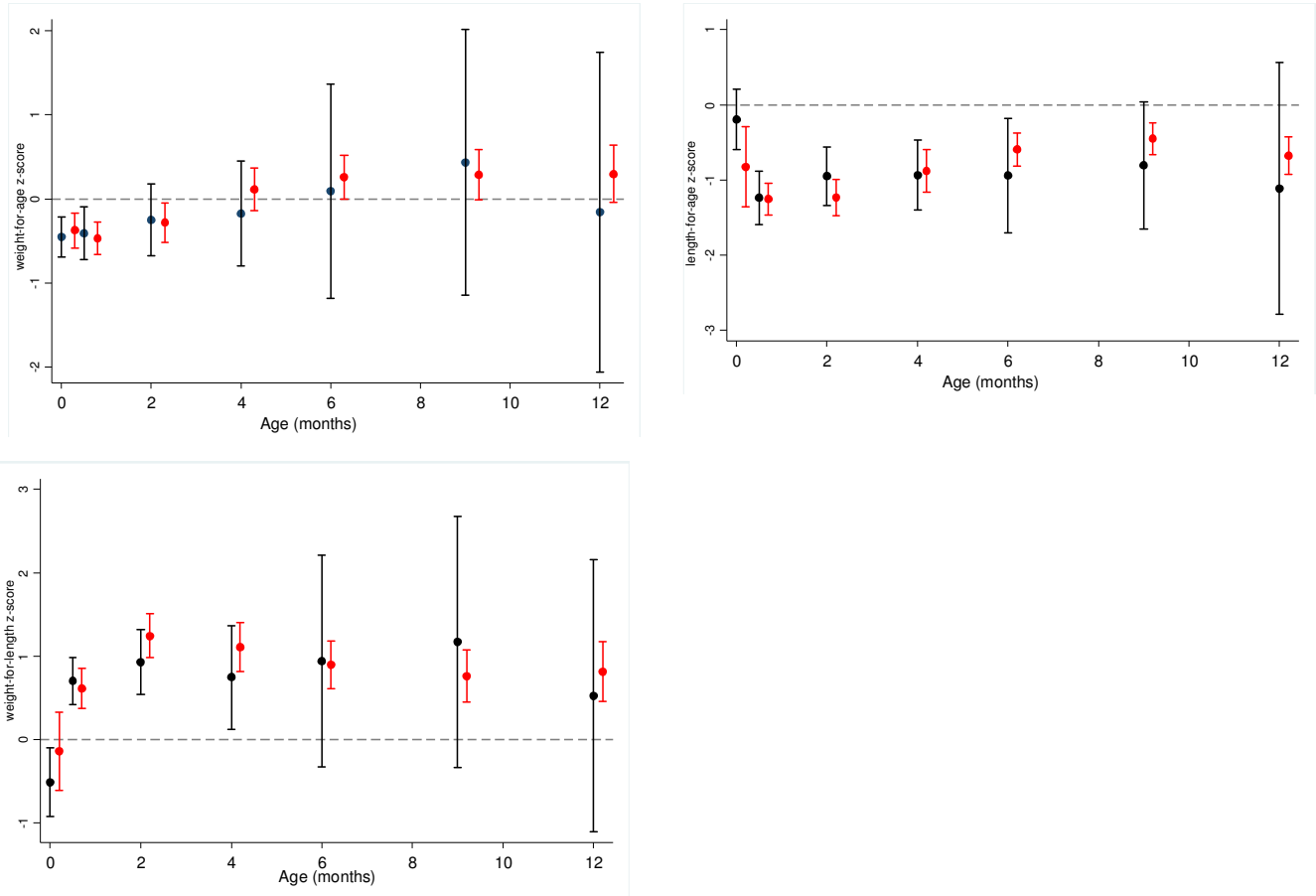
Figure 4.3 Mean and 95% confidence intervals for weight-for-age, length-for-age, weight-for-length z-scores of HIV- exposed uninfected infants by feeding practice (—— breastfeeding, —— formula feeding)

Mixed feeding group, was not included because few women were mixed feeding at each study visit, making the 95% CI too wide.

Table 4.2 Mean (95% CI) WAZ, LAZ, WLZ of HIV-exposed uninfected infants by feeding practise

Age (months)	Predominant breastfeeding			Predominant formula feeding		
	WAZ	LAZ	WLZ	WAZ	LAZ	WLZ
At Birth	-0.46	-0.21	-0.51	-0.37	-0.82	-0.14
	(-0.70 to -.22)	(-0.62 to 0.20)	(-0.93 to-0.09)	(-0.58 to -0.16)	(-1.36 to -0.29)	(-0.61 to .33)
0.5	-0.41	-1.24	0.70	-0.47	-1.25	0.62
	(-0.72 to -0.10)	(-1.60 to -0.88)	(0.42 to 0.98)	(-0.67 to -.27)	(-1.47 to -1.04)	(0.38 to 0.85)
2	-0.25	-0.95	0.93	-0.28	-1.23	1.24
	(-.67 to 0.18)	(-1.34 to -0.56)	(0.54 to 1.32)	(-0.51 to -0.04)	(-1.48 to -0.99)	(0.98 to 1.50)
4	-0.17	-0.94	0.75	0.10	-0.88	1.08
	(-0.80 to 0.45)	(-1.40 to -0.47)	(0.13 to 1.36)	(-0.16 to 0.35)	(-1.16 to -0.60)	(0.79 to 1.38)
6	0.10	-0.94	0.94	0.26	-0.60	0.90
	(-1.18 to 1.37)	(-1.70 to -0.18)	(-0.33 to 2.21)	(0.00 to 0.52)	(-.81 to -0.38)	(0.61 to 1.18)
9	0.43	-0.81	1.17	0.29	-0.45	0.76
	(-1.15 to 2.01)	(-1.65 to 0.04)	(-0.34 to 2.68)	(-0.01 to 0.58)	(-0.66 to -0.25)	(0.45 to 1.08)
12	-0.16	-1.11	0.53	0.30	-0.68	0.81
	(-2.06 to 1.75)	(-2.78 to 0.56)	(-1.11 to 2.16)	(-.04 to 0.64)	(-0.93 to -0.42)	(0.45 to 1.17)

Overall, WVZ ranged from -4.88 to 2.93 in interval 1, -2.03 to 3.10 in interval 2 and -3.50 to 5.81 in interval 3. LVZ ranged from -6.24 to 10.87 in interval 1, -4.56 to 5.08 in interval 2, and -3.09 to 6.79 in the third interval. Mean WVZ differed (p = 0.02) between the feeding groups in the second interval but not in the first and third (Table 4.3). The mean LVZ of predominantly breastfed infants tended to be lower than that of predominantly formula fed infants in the second interval (p = 0.08) (Table 4.3). After adjusting for women's educational level and cART status, mean WVZ (95% CI) of predominantly breastfed infants was -0.70 (-1.31 to -0.09) lower than that of predominantly formula fed infants in the second interval, p = 0.024 but not in first interval with a difference of 0.11 (-0.38 to 0.60), p = 0.66 and in the third interval with a difference of -0.06 (-1.11 to 0.99), p = 0.91. Similarly, the difference in mean LVZ (95% CI) between predominantly breastfed and predominantly formula fed infants were insignificant with a difference of -0.05 (-1.23 to 1.13), p = 0.94, in the first interval, -0.74 (-1.62 to 0.13), p = 0.10, in the second interval and -0.25 (-1.63 to 1.13), p = 0.72, in the third interval.

Table 4.3 Mean velocity Z-scores by age interval and infant feeding practise

	Predominantly breastfed Mean (95% CI)	*n*	Predominantly formula fed Mean (95% CI)	*n*	*p**
WVZ					
Interval 1 (0 – 2) months	-0.09 (-0.56 to 0.38)	31	-0.24 (-0.51 to 0.04)	71	0.57
Interval 2 (2 – 4) months	-0.22 (-0.77 to 0.33)	18	0.49 (0.21 to 0.77)	67	0.02
Interval 3 (4 – 6) months	1.00 (-0.21 to 2.22)	11	1.03 (0.63 to 1.42)	63	0.96
LVZ					
Interval 1 (0 – 2) months	-1.59 (-2.32 to -0.85)	31	-1.57 (-2.29 to -0.84)	67	0.97
Interval 2 (2 – 4) months	-0.61 (-1.09 to -0.14)	18	0.15 (-0.28 to 0.58)	67	0.08
Interval 3 (4 – 6) months	1.22 (0.13 to 2.32)	11	1.51 (0 .99 to 2.04)	68	0.67

*t-test *p* values for group comparisons

Infection-related hospitalizations

There were 27 infection-related hospitalizations, overall. Five of these occurred among predominantly breastfed infants: (3 infants were hospitalized once and 1 was hospitalized twice), and 22 occurred among predominantly formula fed infants (15 infants were hospitalized once, 2 were hospitalized twice, and 1 was hospitalized thrice). Most of the hospitalizations were due to lower respiratory tract infections and diarrhoeal disease. Of the 20 lower respiratory tract infections, 3 were among predominantly breastfed infants. There were 10 diarrhoeal diseases among predominantly formula fed infants. No infections were recorded during a time infants were mixed fed. Predominantly breastfed infants were exposed to breast milk for a total of 168.31 months. Predominantly formula fed infants were exposed to formula milk for a total of 828.45 months and mixed fed infants for 8.08 months. The unadjusted incidence rate of infected-related hospitalizations was 30 per 1000 months of predominant breastfeeding and 27 per 1000 months of predominant formula feeding. The unadjusted odds of infection-related hospitalizations among predominantly breastfed children were 27% lower compared to the odds of predominantly formula fed infants, OR 0.73 (95% CI: 0.26 to 1.99), *p* = 0.53. After adjusting for woman's educational level, cART status, and infant age, the OR was 0.95 (95% CI: 0.33 to 2.74), *p* = 0.92.

The evidence was therefore insufficient to reject the null hypotheses that HIV-exposed uninfected infants on predominantly breastfeeding had similar growth z-scores and infectious morbidity to predominantly formula fed infants.

Discussion

We found that, despite, women being on cART or their infants on ARV prophylaxis and the recommendations favouring breastfeeding, few HIV-infected women chose this option, and among those who did, many switched to formula feeding early. More HIV-infected women

switched to predominant formula feeding than HIV-uninfected women; however, the proportion of HIV-uninfected women who switched to predominant formula feeding was relatively high. Doherty et al., 2012 reported similar findings in South Africa, where 20% and 40% of HIV-uninfected and HIV-infected women had stopped breastfeeding at 3 months, respectively (119). There seem to be diverse experiences in different settings. In Botswana for example, where formula feeding policy was supported for about 1.5 decades, there is supporting evidence indicating acceptability of breastfeeding by HIV-infected women (4). The reasons why women in our study stopped breastfeeding are not clear. In a separate qualitative evaluation of a sub-set of these subjects (described in Chapter 5) we found that women were confused and constantly feared that their child may contract HIV through breast milk because of conflicting messages they received from healthcare providers, possibly explaining why some women stopped breastfeeding. These findings suggest that all women, irrespective of their HIV status need to be educated that breastfeeding is the feeding of choice in this setting. HIV-infected women should be educated that cART and adherence to treatment would make breastfeeding safe. Adopting feasible strategies such as the home visit by community health workers model suggested by Tomlinson et al., 2014 may improve adherence to prolonged breastfeeding (120). A few women were mixed feeding at some point, placing their infants at risk for HIV infection (121).

Predominantly breastfed infants had poorer weight velocity compared to predominantly formula fed infants in the 2 to 4 months age interval. The higher caloric density due to micronutrient and macronutrient content of formula milk and adequate formula milk supplies may have contributed to better growth velocity of predominantly formula fed infants. McGrath et al., 2012 attributed caloric density of formula milk to the slower decline in length growth among formula fed infants compared to breastfed infants (122). It is also plausible that the short duration of exclusive breastfeeding may have contributed to poorer weight velocity of predominantly breastfed infants. About 60% (3 of 5) of the infection-related hospitalizations among predominantly breastfed infants occurred during the 2 to 4 months age interval and this coincided with the time most infants were started on other liquids and solid based foods (median duration of exclusive breastfeeding was 1.9 months). These findings suggest that infants may be vulnerable during the age 2 to 4 months as they are started on other foods that may be contaminated and subsequently increasing their exposure to infectious morbidity that may result in suboptimal growth. Supporting findings were also reported in other settings, for example in Malawi where early weaning was significantly associated with reduced weight velocity and increased morbidity (123). A randomized trial in Zambia reported a significant decrease in WAZ scores among HIV-exposed uninfected infants who stopped breastfeeding at 4 months (3). Our findings differed with those of Kindra and

colleagues who found significant weight gain among breastfed infants compared to formula fed infants (112). High rate of exclusive breastfeeding, prolonged duration of breastfeeding and additional health interventions may have contributed to better weight gain among breastfed infants in that study (112). The benefits of breastfeeding are known to be influenced by the duration and frequency of breastfeeding. Our findings highlight the importance of monitoring breastfeeding practices of HIV-infected women and growth of their infants, especially during the first 12 months of life.

Not surprisingly infection-related hospitalizations tended to be fewer among predominantly breastfed infants compared to predominantly formula fed infants. However, these findings were not statistically significant. There were few infection-related hospitalizations in our study overall, the duration of exclusive breastfeeding was short and the study sample was small; these are likely to explain part of the minimal protective effect of breastfeeding against common infections found in our study. The subsequent switch from breastfeeding to formula feeding by women made it harder to draw conclusions on the role of breastfeeding for HIV-exposed infants in primary healthcare settings. Our growth velocity results need to be interpreted with caution because of the small sample sizes, only infants who attended both study visits in question for a specific age interval were included in the analysis for this outcome. Although our study showed no effect of breastfeeding in preventing infections, studies conducted in controlled settings, demonstrated a protective effect.

Our study described a unique transition of a dual infant feeding system and showed confusion caused among healthcare providers who had to advise and HIV-infected women who had to make a difficult choice. Subsequently, HIV-infected women who chose to breastfeed switched to formula feeding early and the overall effect of predominant breastfeeding on reducing infectious morbidity was minimal and insignificant. These factors distinguish this study from prior studies.

Our study had several limitations. The study had challenges of inadequate enrolment and high early attrition rate that was not expected. In addition, few HIV-infected women chose the breastfeeding option. Only 98% of the enrolment target was reached (184 of a targeted 188 HIV-infected women and their infants; breastfeeding group (n = 80), formula feeding group (n = 104)) following extension of the enrolment from 9 to 18 months. Financial constraints limited further extension of enrolment period. Of the 184 HIV-infected women and their exposed infants, only 121 (breastfeeding (n = 50), formula feeding (n = 71)) with at least one follow-up visit were included in the analysis. The study team attempted to increase participants' attendance of study visits. Strategies included considering participants' personal schedules when setting study appointments, offering free doctor consultations, appropriate

referral to specialized clinics for infants who required special care, and remuneration of R100 (~US$10) at each follow-up visit to compensate for their time. This marked deviation in allocation of groups could have significantly reduced the power of the study to find any differences between predominantly breastfed and formula fed infants should there have been any true differences in infant growth and risk for infectious morbidity. The small sample size due to high attrition rate reduces our confidence to draw any definite conclusions from this study for differences in infant growth and risk of infectious morbidity between predominantly breastfed and formula fed HIV-exposed uninfected infants. Although we have no obvious reason that the infant growth rate and rate of infection-related hospitalization observed in the cohort that continued in the study would have been different from infants who did not continue with the study, attrition bias cannot be ruled out. We may not have found important clinical difference in infectious morbidity between breastfed and formula fed infants because the analysis focused on severe infections requiring hospitalizations. It is plausible that any pattern may have emerged should less severe infections at sick clinic visits had been included. Furthermore, we may not have found important clinical differences in infectious morbidity between breastfed and formula-fed infants due to exclusion of the infants at higher (infants <2000g and <36 weeks gestation at birth). This was done with intent to determine whether there is evidence of a difference for infant feeding practices other than other factors that determine risk for postnatal growth failure and infectious morbidity. We acknowledge that there is a potential for unmeasured and residual confounding because the study could not conducted in a randomized fashion, due to ethical implications of randomly assigning feeding behaviour. Infant feeding practices could have changed between follow-up visits, and the study may not have been able to capture these changes given the dynamics and complexity of infants feeding practices. Poor adherence to breast feeding was the most important unanticipated observation.

The primary objectives of this study were to: a) describe infant feeding practices of HIV-infected women, b) compare breastfeeding feeding patterns of HIV-infected and HIV-uninfected women, c) assess the effect of predominant breastfeeding and formula feeding on attained growth, growth velocity and infectious morbidity among HIV-exposed uninfected infants, over a 12 months period. In conclusion, many women stop breastfeeding early, despite the recommendations favouring breastfeeding. The Western Cape PMTCT program urgently needs strategies that promote and sustain continued breastfeeding by women, to levels that would result in a significant impact on the health of their children. The strategies should be guided by social and contextual factors affecting women's feeding practices.

Chapter 5

An interactive qualitative analysis on HIV-infected mother's decisions between breast- and formula feeding in South Africa – Information, fears, family and friends

Abstract

Introduction
As prevention of mother-to-child HIV transmission programs transition to universal lifelong combination antiretroviral treatment, breastfeeding is becoming more common than formula feeding, in South Africa. The aim of this sub-study was to explore HIV-infected women's experiences and perceptions on breastfeeding and formula feeding.

Methods
Two separate focus group discussions of, a) breastfeeding- (n = 7) and b) formula feeding HIV-infected women (n =8) were conducted in November-December 2013 at Children's infectious diseases clinical research unit, in Tygerberg academic hospital. Women reflected and wrote words describing their infant feeding experiences. Based on focus group responses, we conducted in-depth individual interviews (n = 23) to explore the personal meaning women attached to their feeding experiences. Data were analysed through interactive qualitative analysis.

Results
Study findings revealed two main themes. Theme one consisted of multiple (often competing or contradictory) influences that persisted beyond initiating either choice. The influences pushed and pulled women towards both feeding options. Theme two described three main interacting processes influencing women's decision to either breast- or formula feed; information loops and incremental exposure to "feeding advice", fear of making the "wrong" choice for their infant, and expectations, demands and responses from family and friends. These processes continued after the women had made a particular feeding choice. There were continual pressures which may explain some women's periodic switching between breast- and formula feeding.

Conclusion
In conclusion, HIV-infected women were confused because of conflicting information they received from healthcare providers. There is an urgent need to engage and reorient HIV-infected women, their families, the community and healthcare providers, about the rationale, and reasons for changes in infant feeding guidelines. Infant feeding guidelines for HIV-infected women should integrate considerations of contextual and social issues affecting women's infant feeding practices.

Introduction

In 2013, there were about 3.6 million children younger than 15 years of age living with HIV, globally (124). Most (91%) of HIV-infected children live in sub-Saharan Africa. Approximately 266 000 infants below 2 months of age were HIV exposed in South Africa in 2011, and about 4 800 (2.8%) of these were HIV-infected (125). In 2013 approximately 10 000 new infections were estimated for children younger than 14 years of age in South Africa (126).

Infant feeding in low-resourced settings with high HIV prevalence is a public health concern due to the risk of vertical transmission of HIV, especially in settings where breastfeeding is a social norm. Infant feeding guidelines are rapidly evolving to find the most appropriate infant feeding option for HIV-infected women in these settings. The revised WHO infant feeding guidelines recommend HIV-infected pregnant women receive cART, until at least one week after cessation of breastfeeding or after delivery when formula feeding (8,9). HIV-exposed infants on breast milk are recommended to receive once-daily NVP prophylaxis until they are fully weaned. Formula-fed infants should receive 4-6 weeks of daily NVP or twice-daily AZT.

As PMTCT programs transition towards universal lifelong cART and promoting breastfeeding for HIV-infected women, we hypothesized that rates of breastfeeding would increase and formula feeding would decrease for HIV-infected women in the Western Cape Province of South Africa. Research efforts on infant feeding for HIV-exposed infants have mainly focused on medical and nutritional outcomes (11,127). Subsequently, much attention has been given on the clinical outcomes in development and implementation of infant feeding guidelines, while social and contextual factors have largely been neglected; consequently underestimated in the dynamic of infant feeding behaviours (13). Failure to understand social and contextual factors affecting women's infant feeding practices could therefore compromise uptake of recommended infant feeding options.

The aim of the qualitative study was to explore HIV-infected women's experiences and perceptions on breastfeeding and formula feeding. The qualitative study was conducted about 2 years after the Western Cape PMTCT program started transitioning to providing all women with lifelong cART and promoting breastfeeding. Healthcare providers received within departmental training on counselling HIV-infected women on the importance of breastfeeding. The study compared the feeding experiences of breastfeeding and formula feeding HIV-infected women.

Methods

Participants

A sub-sample of HIV-infected women participating in the longitudinal Mother-Infant Health cohort study was invited to participate in a breastfeeding and formula feeding focus group

discussion and individual qualitative interviews. HIV-infected women who were followed-up for at least 6 months post-delivery in the longitudinal cohort were eligible to participate in the qualitative study. Study participation was not restricted by women's language. The women were contacted by telephone and invited to participate. The aim of the qualitative study was to explore HIV-infected women's experiences and perceptions on breastfeeding and formula feeding during a time the Western Cape PMTCT program was transitioning to providing all HIV-infected women with lifelong cART and promoting breastfeeding. The sub-study was conducted between November-December, 2013.

Focus group discussions were conducted separately by feeding modality (i.e. breastfeeding or formula feeding) and took about four hours to complete. Individual interviews were each approximately 1 hour in length. Focus group discussions and individual interviews were conducted at KID-CRU, in Tygerberg Academic Hospital. All discussions and interviews were audio-recorded. Verbal consent to participate in the sub-study was obtained.

Sample

A total of 38 (breastfeeding (n = 15), formula feeding (n = 23)) women were invited to participate in the qualitative study, of these 8 refused to participate. Seven breastfeeding and eight formula feeding women participated in focus group discussions and twenty-three participated in the individual interviews (eleven of whom were breastfeeding). Among those who participated in the individual interviews, three formula feeding and five breastfeeding women had participated in the focus group discussions. Sample sizes for the focus group and individual interviews were adequate to identify factors associated with infant feeding practices and relationships among the factors, respectively (113). Northcutt and McCoy, (2004), authors of the Interactive Qualitative Analysis methods used for the qualitative study suggest that focus group representation should include 12 to 20 participants (113). The authors also comment that small focus groups are not a serious problem during identification of factors describing their experiences with a certain phenomenon under study but may only skew data when looking at relationships between the factors. Overall, the mean (SD) age of infants of women who participated was 10 (3.11) months. See Table 5.1 for baseline characteristics of participants.

Table 5.1 Baseline Characteristics of women who participated

Characteristic	Focus group		Individual interviews	
	Breastfeeding	Formula feeding	Breastfeeding	Formula feeding
N	7	8	11	12
Age in years, mean (SD)	30.7 (3.3)	27.9 (4.6)	29.6 (4.5)	27.3 (6.3)
Marital status				
Never married	2	8	5	10
Married	3	---	5	2
Widowed/separated	2	---	1	----
Race				
Black African	6	7	9	11
Mixed race	1	1	2	1
Educational level				
Primary	1	1	1	---
Secondary	6	7	10	12
Language				
Xhosa	4	5	8	8
Afrikaans	1	2	2	1
Other African	2	1	1	3
Disclosed HIV status				
Yes	7	7	10	11
Disclosed HIV status to*				
Husband/partner	4	3	7	8
Maternal parents	1	2	2	4
Paternal parents	---	1	1	1
Friends	1	---	---	2
Other	1	4	2	3

*Some women had disclosed their HIV status to more than one person

Study design: Interactive Qualitative Analysis

We used an IQA method. HIV-infected women close to a phenomenon under study (infant feeding experiences in this case) described, labelled their experiences. Women articulated perceived relationships among their experiences to produce a system influence diagram (mental model) representing how the women understood their infant feeding experiences (113). The method uses Systems Theory (114) to conceptualize a phenomenon as comprising a system of factors and relationships among the factors. The factors in IQA research represent categories of meaning from a group sharing a common experience on an issue. To understand a system, the factors of the system and relationships among the factors are identified and described. Focus group discussions are used to identify the factors. The focus group participants are asked to silently reflect and write their experiences, thoughts, beliefs and feelings on the issue under study (113). Relationships reflect participants' perceptions of the relationship among the factors.

Focus group discussion

Group discussions were facilitated by a trained counsellor and three research trainees (including myself). The discussions were conducted in Xhosa, English translations were made for non-Xhosa speaking women and research trainees. The counsellor explained the purpose of the study and the activities the participants would perform during the discussions. The research questions were presented as issue statements. The issue statement for breastfeeding women was: "Tell me your experiences with breastfeeding your baby. Reflect on all thoughts you had concerning the feeding experiences." The issue statement for formula feeding women was: "Tell me your experiences with formula feeding your baby. Reflect on all thoughts you had concerning the feeding experiences."

HIV-infected women openly expressed their experiences, thoughts and emotions that were involved from the time of counselling about safe infant feeding during routine antenatal clinic visits until the focus group discussion. Thereafter, women wrote their infant feeding experiences, feelings, thoughts and concerns, on cards, as short phrases, one experience per card. Once completed, the cards were taped on a wall. The facilitator read aloud the contents of each card and guided participants in clarifying their understanding of the responses on each card to eliminate any ambiguity associated with the meanings of the words or phrases. The group had to reach consensus on the meaning of each card's contents with the purpose of arriving at a socially constructed, shared meaning of the contents of each card among the participants.

Assisted by facilitators, participants reviewed all the cards on the wall and clustered them into factors or common themes. When the majority of the cards were clustered, the facilitators helped participants to identify an appropriate label for each cluster. Any cards that were miscategorised were sorted into appropriate category.

Individual interviews

Individual interviews for breastfeeding women were guided by factors that emerged from the breastfeeding focus group discussion, and similarly for formula feeding women. With assistance of a trained counsellor I shared the focus group's description of each factor with the individual woman and then engaged in a dialogue to explore the personal meaning and life history experiences of the woman on the factor. The following issue statements were presented during the interviews: "The focus group identified several themes describing their infant feeding experiences. Let's look at these themes one at a time while you tell me about your experiences on each of the themes. "The focus group described theme "A" as "Reflecting challenges women face with breastfeeding….." Tell me your experience, opinion, values or feelings with theme A". Participants' key phrases describing their experiences were recorded.

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Participants also described the relationship between the factors identified in the focus group discussions. This was facilitated by asking the participant to speak about the three possible types of relationships between each pair of 'factors' as follows: A influences B (A→B), B influences A (A←B), or no clear relationship (A<>B). During interviews, this exercise was presented as follows: "Look at A and B, as you think about what you have said about these factors, do you see a direct connection between these two or some sort of influence between these two? Explain why you believe so or would you give an example from your own experiences, opinion, values or feelings with the relationship between A and B". Exploring participants' perceptions of relationships between 'factors' enabled a deeper understanding of how they experienced infant feeding.

Factor Description and Analysis
Two translators translated the audio transcripts into English, and back translated to validate the translations. The principal investigator and co-author (GH) were involved in writing the composite descriptions; discrepant descriptions were resolved through discussions. Quotes gathered from index cards that were generated by focus group participants, and transcripts of the focus group discussions were used to develop composite descriptions to illustrate the range of meaning for each factor. This was supplemented by the individual interviews resulting in rich descriptions for each factor.

A summary description of the factors describing HIV-infected women's infant feeding experiences was generated separately for women who breast- and formula fed. The SIDs (113) served as graphical representations of the system of factors and relationships among the factors describing women's experiences. The SIDs served as a basis for further thematic analysis of women's experiences relative to understanding their decision between breast- and formula feeding.

Results
A number of factors influencing HIV-infected women's infant feeding practices were identified during the focus group discussion. There were three interacting processes influencing women's decision to either breast- or formula feed.

1. A general understanding of women's experiences of whether to breast- or formula feed

The decision to breast- or formula feed was on-going as the pressures influencing the women's decision persisted beyond initiating either choice. Women had to make these decisions in the context of multiple (often competing or contradictory) influencing factors (see Figure 5.1)
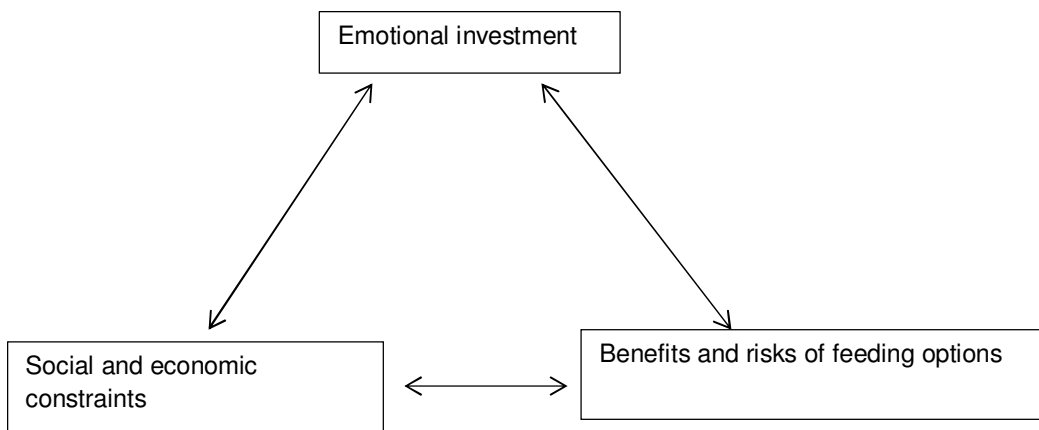
Figure 5.1 Factors influencing HIV-infected women's decision to breastfeed or formula feed

(a) Women's emotional investment

Women were highly emotionally invested in their infant feeding practice. They became worried about people's reactions to their practice. At the same time they wanted to make the right choice for their infants. In the quote below, the woman's relief at being able to escape what would be an emotionally charged decision to formula feed was evident:

> "People encourage you to breastfeed when you do not want to. I was told that I am HIV positive during pregnancy. I was hurt because I knew that I was not going to breastfeed. I was scared that my friends and family members were going to laugh at me, they were already asking about breastfeeding. I had menstrual problems until I gave birth; I had planned to tell them (friends and family members) that was the reason why I was not breastfeeding. When I found out at the clinic that I can breastfeed, I was very happy." (Breastfeeding woman)

Conversely, a woman who elected formula feeding describes the importance of emotional support from her partner in making this decision: *"I was afraid to formula feed because of people. My partner encouraged me to formula feed"* (Formula feeding woman).

(b) Influence of multiple factors

Women expressed confusion, frustration and dissatisfaction at the perceived number of (often competing or contradictory) factors influencing their practices. The factors included:

1. Advice on infant feeding. Women received advice both from within and outside the healthcare system, either supporting or against a particular feeding option.
   "Nurses and counsellors said that it is good to breastfeed because breast milk protects against infections like diarrhoea. They also said that there is a risk that the

baby may get HIV infection. I did not use that advice (to breastfeed) because I was scared to transmit the HIV infection" (Formula feeding woman).

Another woman, who decided to breastfeed, described how important clear, non-contradictory advice from healthcare providers was important to her decision:

"At first I did not know that I can breastfeed when I am HIV positive. I wanted to formula feed my baby. I was advised at the clinic that breastfeeding is the best as the baby would not get illnesses like diarrhoea easily. The encouragement I got from the clinic gave me assurance that my baby would be safe, I then decided to breastfeed." (Breastfeeding woman)

2. Accurate understanding of risk.

Women's own understanding of preventive measures to reduce the risk of vertical transmission of HIV, awareness of HIV status of children who were on a specific feeding modality and perceptions about the risk of vertical transmission of HIV through breast milk were different. Together, their understanding of these issues pushed and pulled women towards both feeding options. These understandings also interacted with the advice women received from healthcare providers and significant others. The following quote illustrates how for one woman, her vicarious experience was more important than any information she receives:

"I chose to formula feed because the bottle is 100% protective and the baby will not be HIV infected. My neighbour is HIV positive, she was breastfeeding and her baby got TB. I knew that if I breastfeed, my baby will be infected. Breast milk is good for those who are HIV negative." (Formula feeding woman)

3. Risk benefit ratio.

The non-HIV related health benefits of either feeding option were in some cases perceived to be in conflict with the HIV-related health risks. In this way, deciding on an infant feeding option was perceived as a compromise between general health benefits and HIV transmission risk.

"From the time I was pregnant, I always wanted my baby to be healthy. I like breastfeeding because a breastfed baby is different (healthier) from a formula fed baby. I was told at the clinic that if you formula feed, the baby is more at risk for illnesses like diarrhoea but when you breastfeed, you know you are giving the best." (Breastfeeding woman)

(c) Constraints of social and economic realities

Women reiterated the social constraints or benefits of each feeding option, describing their feeding practices within real limits. Social stigma was an important factor that forced women to choose breastfeeding they were not comfortable with. Women expressed their view about people's perceptions about women who formula feed: *"Most of the people think that if you are HIV positive, you can't breastfeed. When you are formula feeding, people think you are HIV positive."* (Formula feeding woman)

Similarly women's practices were often dependent on economic constraints which included lack of money to buy food, for example this woman's 'choice' to formula feed (at a time when formula milk was still supplied free of charge by the PMTCT program) was not a choice but the only option given her own lack of food:

> *"I chose formula feeding because there is no food at home. I was afraid that my baby was not going to survive or would starve."* (Formula feeding woman). For some women, the constraints were work related*; "I chose formula feeding because I am working and I do not have enough time to express breast milk."* (Formula feeding woman)

2. A dynamic process that resulted in some women breastfeeding and others formula feeding.

While almost all women experienced the infant feeding practice as a complex and recurring decision, some women ended up breastfeeding and others formula feeding. There were three main processes directing women either way; feeding information and feedback, fear of making the 'wrong' choice for their infant, and lastly, expectations, demands and responses from family and friends. These processes were on-going and continued after the women had made a particular feeding choice. Based on women's emotional reactions and the value women put on multiple influential factors including social constraints, we have the basis for understanding their feeding experiences. There were continual pressures which could explain some women's periodic switching between breast and formula feeding.

(a) Information loops and incremental exposure to 'advice'

Women received advice from within and outside the healthcare system incrementally. For example, during the antenatal period this woman was given information influencing her to breastfeed:

> *"I knew my HIV status in 2012. I did not know what to do. I even wanted to abort the baby because I thought my baby was going to be infected. I went to the clinic and the counsellor explained everything about breastfeeding while you are sick. I*

have adhered to all the procedures they told me until I gave birth. At the clinic they explained to me how breast milk is important for baby's health and for bonding with the baby. The nurses told me that I should not mix feed because of my HIV status and the fact that my baby might get infected." (Breastfeeding woman)

However, after delivery some women were discouraged from breastfeeding by healthcare providers and family members, for example:

"I was initially told to breastfeed for 3 or 6 months. Later, the nurses at the baby clinic told me to stop breastfeeding and said that it would be my fault if the baby gets infected. My family and friends asked me to stop breastfeeding. Even my husband did not want me to breastfeed because we heard people saying that if you breastfeed when you are HIV positive the baby will get infected. They are not talking about the same thing, it is up to you to see if it is going to work or not. I had to select which advice to use." (Breastfeeding woman)

Similarly, women who formula fed described similar experiences with information changing over time, for example this mother described her regret at formula feeding and later learning about the benefits of breastfeeding*: "I heard that it is not right sometimes to formula feed. I regret that I did not breastfeed because I was advised to bottle feed."* (Formula feeding woman)

In general, healthcare providers, family members and friends were the main source of information for breastfeeding women, whereas, formula feeding women received their advice mainly from healthcare providers. A breastfeeding woman explained her personal experience:

"I had decided to formula feed when I was pregnant but when I delivered the nurses advised me to breastfeed because my CD4 count was high and I was happy. I trusted the advice I got from the nurses and I felt my baby was not going to be infected. When one of the mothers taking part in this study told me that her baby became HIV positive, I was very scared to continue breastfeeding, I tried formula feeding but the baby did not like the formula milk. People give you difficult information and it is very stressful." (Breastfeeding woman)

(b) Fear of the wrong decision

For all women, the primary motivation for their infant feeding practice was the health of their child. Women making the decision to breastfeed were plagued by worries that their child may contract HIV. At the same time these women sought emotional affirmation that breast

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milk was better for their baby. Conversely, women who made the decision to formula feed expressed heightened perceptions of the risk of HIV transmission through breast milk, emotionally justifying their practice to give formula milk to their child.

The tension between the knowledge of the risk of vertical transmission of HIV through breast milk, and mothers' desire to choose a feeding option that is optimal for their baby's health played out in every narrative of infant feeding practice. Breastfeeding women had lower perceptions about the risk of HIV transmission through breast milk than women who formula fed. Some described a belief that the risk was low as influenced by feeding practices and health status, as illustrated in this quote: *"I was happy to breastfeed despite my HIV status because my CD4 count was high and I knew that I was going to exclusively breastfeed therefore it was unlikely that my baby was going to be infected."* (Breastfeeding woman)

Some breastfeeding women demonstrated their understanding that antiretroviral prophylaxis needs to be taken regularly:

"I was happy that I was breastfeeding because I knew my baby was getting all the nutrients from the breast milk. I was scared sometimes because I felt like I was a danger to my child. The first day after delivery I could let the baby breastfeed then take the breast out and give it to my baby again because a lot of things were going through in my mind. I got nevirapine and other medication but nurses told me that there is a risk that the baby can get infected. I am not sure if the medication is 100% protective. I always try to take the medication and give the baby his medication so that my baby can be safe." (Breastfeeding woman)

However, for some women concern increased when healthcare providers and significant others discouraged on breastfeeding. As seen in the two quotes below, inconsistencies in the messages made women uncertain about the risks of breastfeeding. Vicarious and personal experiences could cause some women to lose confidence in breastfeeding and (sometimes) switch to formula feeding:

"Sometimes people at the clinic confuse me, some say do not breastfeed and some say breastfeed the baby, the breast never gets sick. This makes me confused because the infection is in my body. I am still confused whether it is good or bad to breastfeed when you are HIV positive. I was scared to continue breastfeeding. Nurses told me to continue breastfeeding but I did not trust them and I stopped breastfeeding. I never breastfed again, I gave my baby formula milk". (Breastfeeding woman)

> *"My second child, whom I breastfed tested HIV positive whilst I was breastfeeding my third child. I thought of stopping breastfeeding my third child."* (Breastfeeding woman)

In contrast, women who decided to formula feed described their perception of the risk of HIV transmission through breast milk as relatively high.

Some women were unhappy about the breastfeeding advice they got from healthcare providers because of health challenges (increase in viral load) they had after initiating breastfeeding, because they felt that they were wrongly informed:

> *"At first I was advised to breastfeed at the clinic and when my viral load was high they advised me to stop breastfeeding, and start formula feeding. I think they just play with our minds at the clinic. They knew my viral load was high and they told me to breastfeed."* (Breastfeeding woman)

(c) Family and friends expectations and demands

Women described the common perception in their community that an HIV–infected woman can only formula feed, and consequently, risking involuntary disclosure of their HIV status or being labelled as "HIV positive". As much as women wanted to make the right infant feeding decision, they also tried to balance between the competing medical and social benefits of each feeding option. However, women who chose breastfeeding and those who chose formula feeding dealt with the two competing issues differently. Subsequently the demands and responses to their decisions were different. Breastfeeding women treated the medical and social benefits of breastfeeding as equally important. While nutritional benefits of breast milk were some of the reasons for wanting to breastfeed, for some the reasons were related to the social limits in which women had to choose their feeding practice. Hence, there were fewer demands from family and friends' on breastfeeding women to explain the reasons why they were breastfeeding, because they had conformed to social expectations of motherhood. Women who formula fed put less value on the social benefits compared to the medical benefits:

> *"Most of the people think that if you are HIV positive you can't breastfeed. When you are formula feeding, people think you are HIV positive. Because I wanted to protect my son from HIV infection I did not care what people were saying."* (Formula feeding woman)

Compared to breastfeeding women, there were more demands from family and friends on women who formula fed to explain their reasons for not breastfeeding. Women responded

differently, some chose not to disclose their HIV status in fear of being discriminated against in the community:

> *"My family asked me where I get a lot of formula milk, and whether I was not sick (HIV positive). I told them that I get the formula from the clinic because my baby does not have a father. I did not disclose because if people know that you are HIV positive, they do not eat your food or come to your house. When I go to the clinic to collect the tins, I go with a big bag and when I throw away empty tins I put them in a plastic so that other people do not see"* (Formula feeding woman).

For those who disclosed, some described positive and others negative social responses:

> *"My brother wanted me to breastfeed, when I told him my HIV status and why I was not breastfeeding, he accepted. He now likes my baby and he says that the baby is growing well."* (Formula feeding woman)

> *"When I knew that I was HIV positive, I told my brother. My brother now keeps swearing at me about my HIV status. We no longer talk to each other because he did not want me to formula feed."* (Formula feeding woman)

The three processes described above were interlinked, at times working in confluence to support women's decision and at others pulling them in the opposite direction. Importantly, the complexities of the three processes were compounded by their interaction, meaning every woman described continual pressures to decide, re-decide, and justify her infant feeding practices.

Discussion

Our findings provide the lived experiences of HIV-infected women wanting to make an appropriate feeding practice for their infants. Women had a range of values which influenced their understanding of the feeding information they received and how they decided on a feeding practice for their infants. Women reacted to their own perceptions of what they felt is best for their infants and to the continual pressures influencing their decisions which persisted beyond initiating either choice.

Healthcare providers either supported or were against a particular feeding option, probably due to their own perception (128). The Tshwane Declaration 2011 and the current feeding recommendations (9) that marked a turning point in support of breastfeeding for HIV-infected women probably resulted in conflicting messages that were shared between the women and healthcare providers. Some of the healthcare providers seem to have adopted an understanding that HIV-infected women can only formula feed, a view that was also common

among HIV-infected women, their families, and the community. Our findings were consistent with those found in settings that did not experience high uptake of formula feeding, for example in Malawi, where healthcare workers found it difficult to advice continued breastfeeding by HIV-infected women (128). Women were then confused and worried that their child may contract HIV through breast milk because of the inconsistent information they received. Furthermore, concerns about HIV-related stigma and continual demands regarding infant feeding practices from families and significant others could have pushed some women to switch between feeding modality. Our results showed the need to refine the quality of infant feeding counselling to avoid possible inconsistences in the messages shared between women and healthcare providers. Besides the medical benefits and risks of either feeding options, infant feeding guidelines need to reinforce contextual and social issues to overcome the challenges women face when making infant feeding decisions.

PMTCT programs adopting a universal breastfeeding policy need to address home food shortages, as a limitation of HIV-infected women's infant feeding practice. The policies need to guide healthcare providers on how to appropriately advise pregnant women in cases were a woman's child from previous pregnancy may have contracted HIV infection through breast milk.

Our findings confirm those of Ijumba and colleagues (129), and provide additional data comparing the experiences of breastfeeding and formula feeding HIV-infected women during a time the PMTCT program was switching from promoting formula feeding to promoting breastfeeding. The findings underscore the importance of regarding infant feeding practice as a social exercise, taking place in a system comprising the HIV-infected woman, the infant, multiple factors and the relationships among these (130,131).

Most of the women were taking cART. However, from our focus group discussions and interviews it was unclear whether women's attitude towards lifelong cART affected their infant feeding practices; we therefore explored this further in the longitudinal cohort study.

Women who formula fed in our qualitative study were more likely to be never married compared to breastfeeding women. Anticipated and real social pressure by family and friends were important in women's decision-making experiences, and never being married seems an important influence on how such social pressures (perpetrated by and in relation to the child's father) influenced the women's decisions. This finding, plus the small sample size of women who participated in the qualitative study, may limit the generalizability of our findings especially to social context where not living with a common law spouse is not often the norm.

In conclusion, HIV-infected women were confused because of conflicting information they received from healthcare providers. There is an urgent need to engage and reorient HIV-infected women, their families, the community and healthcare providers, about the rationale, and reasons for changes in infant feeding guidelines. Infant feeding guidelines for HIV-infected women should integrate considerations of women's interpretation of information about risks and benefits of infant feeding options, formula feeding stigma and the quality of infant feeding counselling affected women's infant feeding practices.

Chapter 6

Summary of findings and conclusions

Brief background and study justification

Finding an appropriate infant feeding option for HIV-infected women in low-resourced setting has been a challenge, in HIV epidemic history. Guidelines on infant feeding for HIV-infected women have changed many times based on new study findings. The most recent changes led to the withdrawal of formula feeding in favour of breastfeeding that has to be continued until 12 months. The changes were informed by studies showing the protective role of breastfeeding against respiratory infections, diarrhoeal disease and better infant growth. The significant reduction in HIV transmission through breastfeeding by cART given either to the HIV-infected woman or infant further strengthened the support for breastfeeding. Many PMTCT programs are now promoting breastfeeding for HIV-infected women, including the Western Cape, where until recently there was high uptake of formula feeding relative to breastfeeding.

Of concern, was that most of the studies informing infant feeding guidelines for HIV-infected women in low-resourced settings were performed under highly controlled conditions, where much effort is put in controlling guideline adherence by investigators and participants. As a result making them less reliable for predicting the real life effects of the feeding options on important clinical outcomes because such efforts are rare in real life practise. Moreover, feeding guideline development and implementation has focused more on medical outcomes but less on social and contextual factors that may relate directly to uptake of the option by HIV-infected women. Importantly, these factors are not well established for the current breastfeeding recommendations. Understanding HIV-infected women's socially constructed views or norms on feeding options, according to our study, provide an insight into how and why the effects of the feeding options in usual care and highly controlled settings are similar or not.

Study objectives and a critique of the rigour of study methods

A longitudinal cohort study reflecting infant feeding practices outside trial settings was performed to provide reliable findings to guide HIV-infected women and healthcare authorities in decision making. The objectives of the longitudinal cohort study were to: a) describe HIV- infected women's infant feeding practices, b) compare infant feeding practices of HIV-infected and HIV-uninfected breastfeeding women c) assess growth and infection-related hospitalizations among predominantly breastfed and predominantly formula fed HIV-exposed uninfected infants in primary healthcare settings, over a 12 months period.

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Women's socially constructed views on breastfeeding and formula feeding were explored in a sub-set of HIV-infected women who were followed-up for at least 6 months post-delivery in the longitudinal cohort. Interactive qualitative analysis methods were used, where women described, labelled their feeding experiences, and articulated perceived relationships among their experiences.

The study designs were determined by their appropriateness for the research questions. The longitudinal cohort study design was appropriate to test theoretical propositions that were expressed in the hypotheses. Women chose their feeding options, to reflect what happens in usual care settings. Any effect of belief in the feeding option the woman chose was acknowledged as a potential mechanism of action whose effect was worth evaluating. The qualitative study provided non-clinical factors explaining the infant feeding practices that were observed in the longitudinal cohort.

Main findings and significance of findings
Despite, the recommendations for breastfeeding, few HIV-infected women chose this option, and among those who did, many switched to formula feeding early. More HIV-infected women switched to predominant formula feeding during follow-up; however, the proportion of HIV-uninfected women who switched to predominant formula feeding was relatively high. These differences were seen from about two weeks, and persisted throughout follow-up. By about 4 months, half of the HIV-infected women had switched to predominant formula feeding. Predominantly breastfed infants were exclusively breastfed for a short duration and had poorer weight velocity compared to predominantly formula fed infants in the 2 to 4 months age interval. There tended to be fewer infection-related hospitalizations among predominantly breastfed compared to predominantly formula fed infants. However, the protection against infections by breastfeeding was minimal and insignificant. Early switching to formula feeding by breastfeeding women is an unintended consequence of the current recommendations as this increase the risks of death due to diarrhoeal disease.

As gained from the focus group discussions and qualitative interviews, it was interesting to note for future guidelines that the dual infant feeding option employed by the Western Cape PMTCT program while transitioning from formula feeding policy to breastfeeding caused confusion among healthcare providers who either supported or were against a particular feeding option because some of them seem to have adopted an understanding that HIV-infected women should only formula feed. This view was also common among HIV-infected women and their families, despite current information on the benefits of breastfeeding. The women had difficulty dealing with opinions of family members and healthcare providers regarding breastfeeding while HIV-infected, possibly explaining why some women stopped

breastfeeding. Women constantly feared that their infants might contract HIV through breast milk, because of the conflicting messages received. In addition, women's own understanding of non-HIV and HIV-related benefits and risks, formula feeding stigma and the quality of counseling affected their decisions on infant feeding practices.

Breastfeeding is now known to be safe for HIV-infected women but as noted from the qualitative interviews, what is important is how to get the message across in new guidelines support for HIV-infected women. We found that HIV-infected women required support with the correct attitudes for breastfeeding. The Western Cape PMTCT program must ensure that healthcare providers follow the principles and guidance provided by provincial infant feeding guidelines to avoid giving conflicting messages. Primary healthcare services are encouraged to provide in-depth training in breastfeeding for all health care staff or develop office practices that promote and support breastfeeding. Education of both HIV-infected women and their families is an essential component of successful breastfeeding.

Our study was unique in that it is the first to describe heterogeneity in infant feeding practices among HIV-infected women during a transition of a dual infant feeding system, outside of a trial setting. The study provides the first data in Western Cape Province to uncover poor adherence to breastfeeding. We were also able to do an in-depth analysis of the effects of these behavioural shifts on infant growth and infection-related hospitalizations. The qualitative aspect also enhanced the findings of the longitudinal cohort as it helped to evaluate in part reasons for women's different infant feeding practices, using a sub-set of the same group of women in the cohort study.

Our study had several limitations. The study had challenges of inadequate enrolment and high early attrition rate that was not expected. In addition, few HIV-infected women chose the breastfeeding option. Only 98% of the enrolment target was reached (184 of a targeted 188 HIV-infected women and their infants; breastfeeding group (n = 80), formula feeding group (n = 104)) following extension of the enrolment from 9 to 18 months. Financial constraints limited further extension of enrolment period. Of the 184 HIV-infected women and their exposed infants, only 121 (breastfeeding (n = 50), formula feeding (n = 71)) with at least one follow-up visit were included in the analysis. The study team attempted to increase participants' attendance of study visits. Strategies included considering participants' personal schedules when setting study appointments, offering free doctor consultations, appropriate referral to specialized clinics for infants who required special care, and remuneration of R100 (~US$10) at each follow-up visit to compensate for their time. This marked deviation in allocation of groups could have significantly reduced the power of the study to find any differences between predominantly breastfed and formula fed infants should there have

been any true differences in infant growth and risk for infectious morbidity. The small sample size due to high attrition rate reduces our confidence to draw any definite conclusions from this study for differences in infant growth and risk of infectious morbidity between predominantly breastfed and formula fed HIV-exposed uninfected infants. Although we have no obvious reason that the infant growth rate and rate of infection-related hospitalization observed in the cohort that continued in the study would have been different from infants who did not continue with the study, attrition bias cannot be ruled out. We may not have found important clinical difference in infectious morbidity between breastfed and formula fed infants because the analysis focused on severe infections requiring hospitalizations. It is plausible that any pattern may have emerged should less severe infections at sick clinic visits had been included. Furthermore, we may not have found important clinical differences in infectious morbidity between breastfed and formula-fed infants due to exclusion of the infants at higher (infants <2000g and <36 weeks gestation at birth). This was done with intent to determine whether there is evidence of a difference for infant feeding practices other than other factors that determine risk for postnatal growth failure and infectious morbidity. We acknowledge that there is a potential for unmeasured and residual confounding because the study could not conducted in a randomized fashion, due to ethical implications of randomly assigning feeding behaviour. Infant feeding practices could have changed between follow-up visits, and the study may not have been able to capture these changes given the dynamics and complexity of infants feeding practices. Poor adherence to breast feeding was the most important unanticipated observation.

Despite, the limitations of our study, we can conclude that all women, irrespective of their HIV status need to be educated that breastfeeding is the feeding of choice in this setting. Strategies to promote and sustain continued breastfeeding by women, that would result in a significant impact on growth and general health of their children are urgently needed. The strategies should be guided by factors affecting women's feeding practices such as women's interpretation of information about risks and benefits of infant feeding options, formula feeding stigma and quality of infant feeding counselling.

Implications for research

The main study aims were to: a) describe infant feeding practice of HIV-infected and uninfected women b) assess the effectiveness of predominant breastfeeding and formula feeding, in improving growth and reducing infection-related hospitalizations of HIV-exposed uninfected infants in primary healthcare settings c) explore HIV-infected women's experiences and perceptions on breastfeeding and formula feeding. Each of these three aims was achieved, though there are new emerging issues worth further investigating. The following research questions are proposed: a) What strategic interventions are needed to

promote and sustain continued breastfeeding by HIV-infected women? b) Could it be that breastfeeding was not well established in this setting such that the protection against infections by breastfeeding was minimal and insignificant, when, in fact, breastfeeding could have been significantly protective?

"The PhD Path: Experience and Lessons Learned"

The critique from journal peer reviewers and during meetings and conference presentations helped me focus my research project, made it more exciting and made me want to work harder. My skills for writing protocols for funding were sharpened as shown by the number of grants obtained. I developed the ability for independent, critical judgement and was able to analyse, understand and describe patterns in my research data rationally and objectively. I acquired the skills to link the conclusions and the theoretical perspectives that guided the research study, thus displaying high level of thinking and reasoning. The timely feedback I received from my promoters helped me to reach my research goals – and that kept me in a happy state.

PhD Profile

PhD Candidate	Moleen Zunza
PhD supervisor	Prof Mark F Cotton
PhD co-supervisor	Prof Monika Esser
PhD period	01/08/2012 to 31/12/2015

	Year
Specific statistics courses Biostatistics Applied stochastic simulation Data mining R programming Multivariate analysis Stochastic models Sampling techniques	 2013 2013 2014 2014 2014 2015 2015
Seminars, workshops	
International Traineeships in AIDS Prevention Studies (ITAPS): Scientific Manuscript Writing Program (University of California San Francisco)	March-June 2015
Interview techniques and analysis (African Doctoral Academy Summer school)	January 2013
Introduction to qualitative data analysis with ATLAS.ti (African Doctoral Academy Summer school)	January 2013
Interactive qualitative analysis methods (Centre for Higher and Adult Education, Stellenbosch University)	October 2012
GRADEing the Quality of Evidence (MRC South Africa)	June 2012
Presentation in meetings, regional and international conferences	
Moleen Zunza, Monika Esser, Mark F. Cotton. Infant feeding choices and effects on infant morbidity in PMTCT programs transitioning to "option B+" in Western Cape, South Africa. Oral presentation, 6th FIDSSA Congress, Drakensberg, South Africa, 5-8 November 2015.	2015
Moleen Zunza, Monika Esser, Mark F. Cotton. Infant feeding choices and effects on infant morbidity in PMTCT programs transitioning to "option B+" in Western Cape, South Africa: The Mother Infant Health Study. Oral presentation, 59th Annual Academic Year Day, Stellenbosch University 13th August 2015.	2015
Moleen Zunza, Gareth Mercer, Mark F. Cotton, Monika Esser, Graeme Hoddinott, Julie A. Bettinger. An Interactive Qualitative Analysis on HIV-infected mother's decisions between breast- and formula feeding in South Africa – information, fears, family and friends. E-Poster presentation, SAPA Congress, Cape town, South Africa, 11 September 2014	2014
Moleen Zunza, Gareth Mercer, Mark F. Cotton, Monika Esser, Graeme Hoddinott, Julie A. Bettinger. An Interactive Qualitative Analysis on HIV-infected mother's decisions between breast- and formula feeding in South Africa – information, fears, family and friends. Poster presentation, 20th IEA World Congress in Epidemiology, Alaska, Anchorage, USA, 17-21 August 2014	2014
Peer reviewed publications	
Moleen Zunza, Gareth D Mercer, Lehana Thabane, Monika Esser and Mark F Cotton. Effects of postnatal interventions for the reduction of vertical HIV transmission on infant growth and non-HIV infections: a systematic review.	2013

Journal of the International AIDS Society 2013, 16:18865	
Moleen Zunza, Gareth Mercer, Mark F. Cotton, Monika Esser, Graeme Hoddinott, Julie A. Bettinger. An Interactive Qualitative Analysis on HIV-infected mother's decisions between breast- and formula feeding in South Africa – information, fears, family and friends (to be submitted to SAHARA)	
Moleen Zunza, Monika Esser, Mark F. Cotton. Infant feeding choices and effects on infant morbidity in PMTCT programs transitioning to "option B+" in Western Cape, South Africa: The Mother Infant Health Study (to be submitted to BMC Paediatrics)	
Grants awarded	
President's Emergency Plan for AIDS relief (PEPFAR) through HRSA under the terms of T84HA21652 (R400 000)	2012 - 2013
Harry Crossley Foundation Project Funding (R40 000)	2011, 2013
Clinical Research Grant, Stellenbosch University (R150 000)	2011
Temporary research assistant grant, Stellenbosch University (R60 000)	2013-2014
South African Medical Research Council Self-initiated Grant (R389 814.50)	2013-2015

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Appendices

Appendix 1:

Effects of postnatal interventions for reduction of vertical HIV transmission on infant growth and non-HIV infections: a systematic review

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Keywords: postnatal interventions; HIV; children; growth; non-HIV infections; breast milk;

Abstract

Introduction: Guidelines in resource-poor settings have progressively included interventions to reduce postnatal HIV transmission through breast milk. In addition to HIV-free survival, infant growth and non-HIV infections should be considered. Determining effect of these interventions on infant growth, and non-HIV infections will inform healthcare decisions about feeding HIV-exposed infants. We synthesise findings from studies comparing breast to formula feeding, early weaning to standard-duration breastfeeding, breastfeeding with extended antiretroviral to short-course antiretroviral prophylaxis, and alternative preparations of infant formula to standard formula in HIV-exposed infants, focusing on infant growth and non-HIV infectious morbidity outcomes. The review objectives were to collate and appraise evidence of interventions to reduce postnatal vertical HIV-transmission, and estimate their effect on growth and non-HIV infections from birth to two years of age among HIV-exposed infants.

Methods: We searched PubMED, SCOPUS, and Cochrane CENTRAL Controlled Trials Register. We included randomised trials and prospective cohort studies. Two authors independently extracted data and evaluated risk of bias. Rate ratios and mean differences were used as effect measures for dichotomous and continuous outcomes, respectively. Where pooling was possible, we used fixed effects meta-analysis to pool results across studies. Quality of evidence was assessed using the GRADE approach.

Results and discussion: Prospective cohort studies comparing breast- versus formula-fed HIV-exposed infants found breastfeeding to be protective against diarrhoea in early life (risk ratio (RR)= 0.31; 95% confidence interval (CI) 0.13 to 0.74). The effect of breastfeeding against diarrhoea (hazard ratio (HR) = 0.74; 95% CI 0.57 to 0.97) and respiratory infections (HR = 0.65; 95% CI 0.41 to 1.00) was significant through 2 years of age. The only randomised controlled trial available showed breastfeeding tended to be protective against malnutrition (RR = 0.63; 95% CI 0.36 to 1.12). We found no statistically significant differences in the rates of non-HIV infections or malnutrition between breastfed infants in the extended and short-course antiretroviral prophylaxis groups.

Conclusions: Low to moderate quality evidence suggests breastfeeding may improve growth and non-HIV infections outcomes of HIV-exposed infants. Extended ARV prophylaxis does not appear to increase the risk for HIV-exposed infants for adverse growth or non-HIV infections compared to short- course ARV prophylaxis.

PROSPERO Number: 'Completed review'

Introduction

Human immunodeficiency virus (HIV) infection among children is a public health concern especially in poorly resourced countries [1]. Most children acquire HIV infection through mother-to-child transmission (MTCT) [2]. Approximately 2.5 million children are living with HIV/AIDS worldwide [3]. Although the proportion of HIV-attributable death among children less than 5 years of age is declining worldwide, HIV/AIDS is still a leading cause of premature death in Southern African children [4]. In the absence of antiretroviral (ARV) treatment, one third of HIV-infected children die by one year of age and about 50% by 2 years of age [4]. Infectious diseases and nutritional complications are the predominant underlying causes of mortality in these children [4].

HIV may be vertically transmitted in pregnancy, labour, delivery, or through breast milk. Without interventions, 15-30% of infants are vertically infected; breastfeeding increases the risk to 20-45% [5]. Strategies to reduce postnatal vertical transmission of HIV focus on reducing transmission through breast milk. HIV-infected mothers in high-income countries are recommended to completely avoid breastfeeding [6]. However, in poorly resourced countries where formula feeding does not generally meet AFASS criteria (Acceptable, Feasible, Affordable, Sustainable, and Safe), avoiding breastfeeding increases the risks of infant mortality and infectious morbidity [7].

Description of the intervention

The efficacy of ARV regimens in reducing HIV vertical transmission through breast milk has been demonstrated in several randomised controlled trials (RCTs) [8-11], these interventions have since been incorporated into the World Health Organization (WHO) guidelines on infant feeding by HIV-infected mothers [12].

WHO 2013 prevention of MTCT (PMTCT) guidelines recommend that all HIV infected pregnant women receive highly active ARV treatment (HAART), until at least one week after cessation of breastfeeding or after delivery when formula feeding, but should preferably be continued as life-long therapy regardless of CD4 count [12]. Mothers with CD4 count ≤ 500cells/mm^3 or WHO clinical stage 3 or 4 disease are recommended to continue lifelong ARVs. HIV-exposed infants on breast milk are recommended to receive once-daily nevirapine (NVP) prophylaxis until they are fully weaned. Formula fed infants should receive 4-6 weeks of daily NVP or twice-daily Zidovudine (ZDV) [12].

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Effect of postnatal MTCT interventions on infant growth and non-HIV infections

Compared to infant formula, breast milk protects against gastrointestinal and respiratory tract infections and improves overall survival [13]. Breastfeeding also promotes optimal child growth until 2 years of age [14].

ARVs drugs minimize postnatal HIV transmission through breast milk by reducing breast milk viral load. As ARVs have clinical and laboratory adverse effects, their safety in HIV-exposed children should be considered. Baroncilli *et al*. reported a high risk of anaemia in HIV-exposed infants exposed to HAART with ZDV alone compared to HAART without ZDV, which disappeared at 1 month of life [15]. Grade 3-4 hepatoxicity was reported in infants exposed to NVP for at least 5 days [16]. Neonatal exposure to Lopinavir/ritonavir (LPV/r) has been associated with cardiac toxicity and adrenal dysfunction [17]. Lamivudine exposure is safe in HIV-exposed infants [18]. While side effects would not negate the benefits of ARVs in preventing HIV transmission, it is important for health policy makers to have accurate estimates of the anticipated risks of such effects when introducing these interventions into clinical practice.

Why it is important to do this review

A Cochrane review appraised evidence for the efficacy of postnatal HIV PMTCT interventions in preventing HIV transmission, and improving HIV-free survival [19]. However, in addition to their efficacy in preventing HIV transmission, policy makers should consider the effects of these interventions on infant growth and susceptibility to non-HIV infections.

Contradictory findings of the effects of different postnatal PMTCT interventions on infant growth and non-HIV infectious morbidity were reported in clinical trials and observational studies; therefore the true effects of the interventions on these outcomes is uncertain. To inform decision-making about HIV PMTCT recommendations, this review aims to synthesize findings from studies comparing the effects of different postnatal interventions for PMTCT of HIV on infant growth and non-HIV infections, with follow-up periods of between 3 to 24 months of age.

Objectives

To collate and appraise evidence of interventions to reduce postnatal vertical HIV-transmission in HIV-exposed infants, and estimate their effect on:

Primary:

Growth from birth to two years of age

Secondary:

Non-HIV infections from birth to two years of age

Methods

Criteria for considering studies for this review

Studies

- RCTs of postnatal interventions to prevent vertical transmission of HIV, which included assessment of infant growth or non-HIV infections.
- RCTs assessing effect of established postnatal interventions for prevention of vertical transmission of HIV on infant growth or on-HIV infections.
- Cohort studies were also included if the intervention (e.g. mode of feeding) could not ethically be randomised.

Participants

HIV-infected mothers and their infants

Interventions

Intervention aimed at reducing HIV vertical transmission.

Primary outcomes

- Weight-for-age (WAZ), weight-for-length (WLZ), length-for-age (LAZ), and head circumference-for-age (HCA) *z*-scores and malnutrition.

- Non-HIV infections e.g. respiratory tract infections, gastrointestinal infections.

Search methods for identification of studies

Electronic searches

Search strategies developed by The Cochrane Collaboration HIV/AIDS Review group were used to search for studies [19]. PubMED (24 April 2013), SCOPUS (24 April 2013), and Cochrane CENTRAL Controlled Trials Register (11 March 2013) were searched without language, time or publication status restrictions (Additional Table 1: Search strategies). Dates indicate the time when searches were last performed in each database. The reference lists of included studies were searched for studies.

Data collection and analysis

Selection of studies

Two reviewers (MZ and GM) independently reviewed abstracts of electronic search results. Full texts of potentially relevant articles were retrieved and independently examined for eligibility.

Data extraction

The following data were independently extracted in duplicate: study design, study duration, methodological quality, study interventions, and outcomes. Discrepancies were resolved through discussion.

Assessment of risk of bias in included studies

The Cochrane Collaboration's risk of bias tool was used to assess the methodological quality of each selected study [20]. Two authors (MZ and GM) independently assessed the risk of bias. The following domains were assessed: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; whether incomplete outcomes data were adequately addressed; selective reporting; and other bias.

ClinicalTrial.gov and Current Controlled trial registries were searched for protocols of included studies. If the protocol was unavailable, the methods and results sections were compared to assess the potential for selective reporting bias.

Measures of treatment effect

When included publications presented summary data separately for each intervention group, we calculated risk ratios (RR) for binary outcomes and mean differences (MD) for continuous outcomes, and associated 95% confidence intervals (CI). Otherwise we have directly presented the effect estimates (RR, hazard ratio (HR), and odds ratios (OR)) reported in the publications.

For infectious morbidity events we assumed that the occurrence of each outcome per participant is a random variable following a Poisson distribution. The normal approximation to the Poisson distribution was used to calculate confidence intervals (CI) for mean differences in incidence of infectious morbidity outcomes. The 95% CI for the mean difference was calculated as:

$$(\widehat{\lambda}_1 - \widehat{\lambda}_2) \pm 1.96 \times \sqrt{\frac{\widehat{\lambda}_1}{n_1} + \frac{\widehat{\lambda}_2}{n_2}},$$ where $\widehat{\lambda}_1$ and $\widehat{\lambda}_2$ are estimated average counts of a specific infection in group 1 and 2, and n_1 and n_2 are numbers of infants with complete follow-up data in each group [21].

Unit of analysis issues

Repeated observations on participants

When results were presented for more than one time point, the following approaches were used to obtain single effect measures:

For infectious events we computed the total number of events experienced during the entire follow-up period for each intervention group. For growth outcomes, summary data were extracted at the longest follow-up time point.

Multiple intervention groups

Experimental intervention groups deemed sufficiently comparable were combined for pairwise comparison with the control group. For dichotomous outcomes, sample size and outcome events were summed across combined groups. For continuous outcomes, means and standard deviations (SD) were combined using the following formulas [20].

$$SD = \sqrt{\frac{(N_1-1)SD_1^2 + (N_2-1)SD_2^2 + \frac{N_1 N_2}{N_1+N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$$

$$Mean = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

Where N_1, M_1 and SD_1 are sample size, mean and standard deviation of group 1, N_2, M_2, SD_2 are the corresponding values of group 2.

Studies using a factorial design

One report was from a trial that used a factorial design [11]. We only report on the effect of antiretroviral interventions in this review. Reports of the study did not suggest an important interaction between the two interventions.

Dealing with missing data

Authors of twelve studies were contacted for missing information; the requested information being obtained for six studies. The potential impact of missing data was considered during risk of bias assessment. Meta-analysis was repeated, excluding studies with attrition rates

>20% to assess the robustness of the results to missing data, and both estimates are presented.

Assessment of heterogeneity

Substantial statistical heterogeneity was defined as an I^2 statistic > 50% [20].

Assessment of publication bias

Too few studies were included in each comparison to enable investigation of publication bias.

Data synthesis

Fixed-effects meta-analysis using the Mantel-Haenszel method for dichotomous outcomes and the Inverse-variance method for continuous outcomes were used to pool results across studies [20]. Where meta-analysis was inappropriate, individual study results were reported separately. Review Manager 5.1 was used for analysis.

Quality of evidence

The Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach was used to rate quality of evidence [22]. In evaluating the quality of RCT evidence, we considered the following in whether to downgrade the quality of evidence: methodological limitations, inconsistency in study results, indirectness, imprecision and publication bias. For observational studies, we considered the following factors in determining whether to upgrade the quality of evidence: large observed effect and whether plausible confounding would change the intervention effect. Our ratings for the breastfeeding versus formula feeding and the breastfeeding with extended versus short-course ARV prophylaxis comparisons are presented in Table 2 and 3, respectively.

Results

Included studies

We identified fourteen reports from 7 RCTs and 3 prospective cohort studies (Figure 1) conducted in: South Africa (3), Zambia (1), Malawi (1), USA and Brazil (1), Cote d'Ivoire (1), Tanzania (1), Kenya (1), Burkina Faso, Kenya and South Africa(1) and South Africa, Tanzania, Uganda and Zimbabwe (1) (Additional Table 2: Characteristics of included studies). Ten studies were excluded on review of full articles (Additional Table 3: Excluded studies).
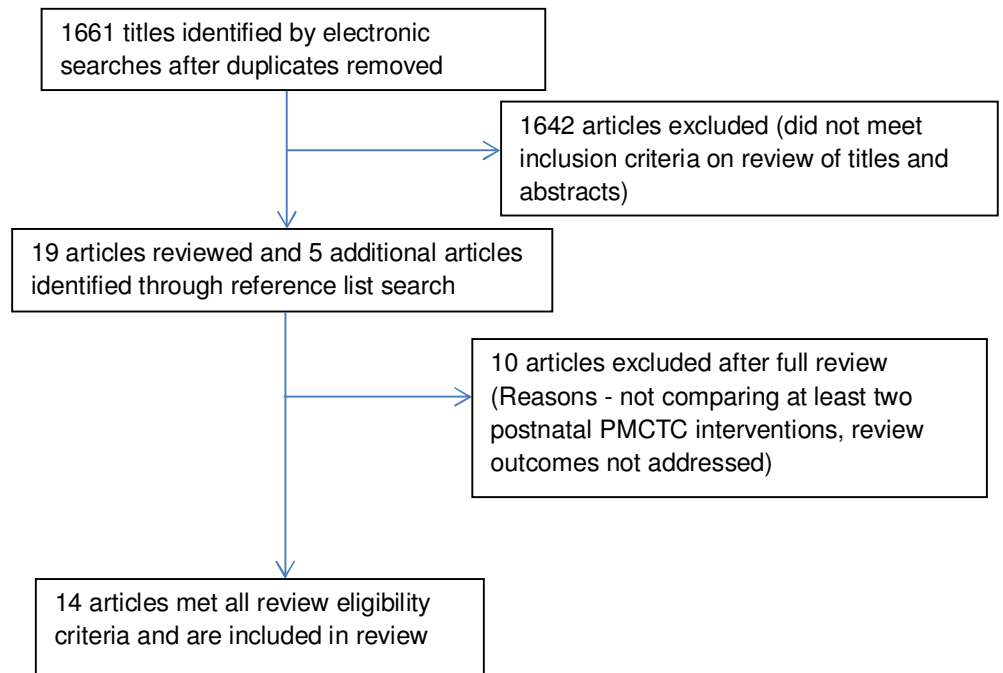
1661 titles identified by electronic searches after duplicates removed

1642 articles excluded (did not meet inclusion criteria on review of titles and abstracts)

19 articles reviewed and 5 additional articles identified through reference list search

10 articles excluded after full review (Reasons - not comparing at least two postnatal PMCTC interventions, review outcomes not addressed)

14 articles met all review eligibility criteria and are included in review

Figure 1. Flow diagram of screening process

Types of interventions

Table 1 summarises the studies included and outcomes assessed under each comparison.

Table 1: Summary of included studies and outcomes assessed for each comparison

Comparisons	Studies (Sample size)	Outcomes assessed	Studies
Breastfeeding vs. Infant formula feeding	4 (1741)	Malnutrition	Becquet *et al.,2007* Mbori-Ngacha *et al.,2001*
		Growth	Kindra et al.,2012
		Respiratory tract infections	Mbori-Ngacha *et al.,2001* Venkatesh *et al.,2011*
		Diarrhoea	Mbori-Ngacha *et al.,2001* Becquet *et al.,2007* Venkatesh *et al.,2011* Kindra et al.,*2012*
Breastfeeding with extended ARV prophylaxis vs. breastfeeding with short course ARV prophylaxis	5 (7956)	Growth faltering	Jamieson *et al.,2012* Kesho Bora 2011 Kumwenda *et al.,2008*
		Pneumonia	Coovadia *et al.,2012* Kesho Bora, 2011 Gray *et al.,2005* Kumwenda *et al.,2008* Kesho Bora, 2011 Jamieson *et al.,2012*
		Gastroenteritis	Coovadia *et al.,2012* Kesho Bora, 2011 Gray *et al.,2005* Kumwenda *et al.,2008* Jamieson *et al.,2012*
		Meningitis	Kumwenda *et al.,2008* Jamieson *et al.,2012*
		Sepsis	Kumwenda *et al.,2008*
Early cessation of breastfeeding vs. standard duration	2(451)	Growth	Arpadi *et al.,2008*
		Prolonged diarrhoea	Fawzy *et al.,2011*

Chemically or biologically acidified infant formula vs. standard infant formula	1(132)	Growth Bronchopneumonia Gastroenteritis	Velaphi *et al.,2008*
Concentrated infant formula vs. standard infant formula	1(1686)	Growth	Winter *et al.,2009*
Chemical acidified infant formula milk with or without prebiotics and nucleotides	1(84)	Growth	Cooper *et al.,2010*

Risk of bias in included studies

The risk of bias summary presents authors' judgments on risk of bias in each domain for each study separately (Figure 1), while the risk of bias graph presents the risk of bias in each domain as a percentage across all included studies (Figure 2). A summary of our findings on study methodological quality for each domain follows below.

Allocation (selection bias)

Random sequence generation was adequate in 10 studies [9] [11] [23-30]. The method of sequence generation was not reported in 1 study [31]. Risk of bias was high for 3 observational studies because participants self-selected into comparison groups [32-34].

Methods of allocation concealment were adequate in 10 studies [9] [11] [23-27] [29-31]. One study did not report how treatment allocation was concealed [28]. The risk of bias in this domain was high for the 3 observational studies [32-34].

Blinding (performance bias and detection bias)

Participants and personnel (performance bias)

Seven studies were assessed as having low risk of participant performance bias [9] [11] [24] [26,27] [30,31]. Five studies were at high risk because participants were unblinded and it was felt that knowledge of their intervention allocation, rather than the intervention itself, could have affected participants' outcomes [23] [25] [28] [33, 34]. Two studies were unclear on whether participants were blinded [29] [32]. Risk of personnel performance bias was low in 8 studies [9] [11] [23, 24] [26, 27] [30, 31]. Two studies were at high risk because personnel may have treated participants differently through knowing their intervention

allocation, thereby influencing the outcomes [25] [33]. It was unclear in 4 studies whether personnel were blinded [28, 29] [32] [34].

Outcome assessment (detection bias)

Risk of detection bias was judged to be low in 10 studies [9] [11] [23- 27] [31] [33, 34]. One study was at high risk because outcomes were ascertained through participants' verbal reports and outcome definitions were relatively subjective [28]. It was unclear whether outcome assessors were blinded in three studies [29,30] [32].

Incomplete outcome data (attrition bias)

Seven reports with an attrition rate below 20% were judged to have low risk of attrition bias [9] [11] [27- 30] [33]. Five reports were judged high risk [23] [26] [31, 32] [34], and 2 studies were unclear [24, 25].

Selective reporting (reporting bias)

Protocols were available for five studies [9] [11] [23] [27] [30]. Nine reports were at low risk of reporting bias [11] [25- 30] [32] [34]. Three reports were at high risk, because either not all study results were reported at pre-specified time points or the reported outcome was not pre-specified in the protocol [9] [23, 24]. Risk of bias due to selective reporting was unclear in two studies [31] [33].

Other sources of bias

Nine studies were judged low risk of other bias [9] [25- 30] [32] [33]. One study was at high risk, the data safely monitoring board recommended enrolment of controls be stopped early because of an apparent intervention benefit [11]. Risk of other bias was unclear in 4 studies; either baseline characteristics were not compared between study arms, there was a potential for misclassification of exposure status or the role of the funder was not described [23,24] [31] [34].

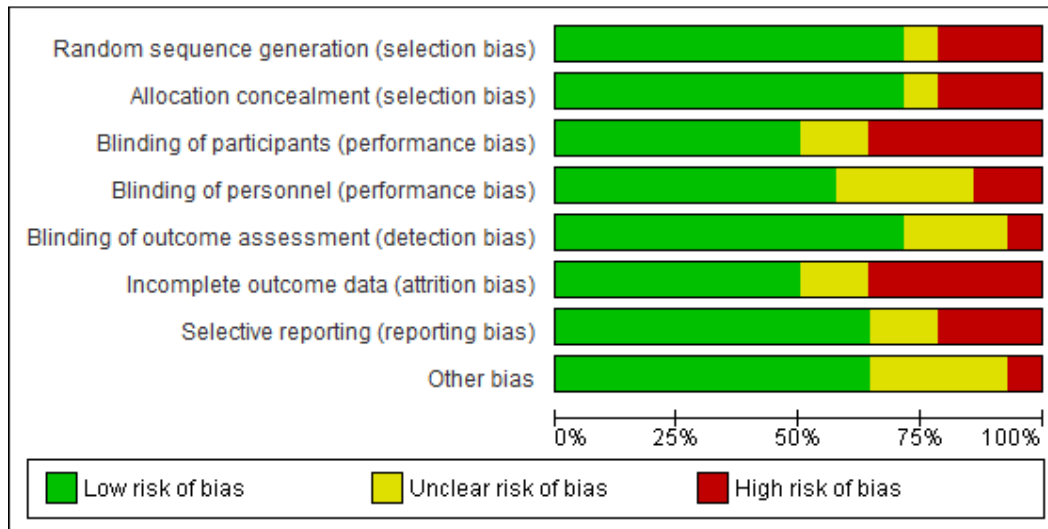**Figure 1.** Risk of bias for each domain per study

Figure 2. Risk of bias graph for each domain across all studies

Effects of interventions

Except where specified, results are from combined data from HIV-infected and HIV-uninfected infants. Wherever publications presented findings separately for HIV-uninfected infants we report these. For characteristics of included studies see Additional Table 1.

1. Breastfeeding versus formula feeding

One RCT [28] and three prospective cohort studies [32- 34] compared growth and non-HIV infections outcomes between breast and formula fed HIV-exposed infants. We report the RCT and cohort studies separately.

Mbori-Ngacha *et al.* randomly assigned mother-infant pairs to breast or formula feeding groups [28]. Cumulative HIV-infection rates by 2 years of age were 37% and 21%, respectively.

Becquet *et al.* compared infants whose mother chose breastfeeding with rapid transition to formula feeding after 4 months of age to infants whose mothers chose exclusively formula feeding [32]. HIV transmission rates at 18 months were 5% and 1% among breast and formula fed infants, respectively.

Kindra *et al.* compared outcomes of infants whose mothers elected to either breastfeed or formula feed. By 6 weeks of age, HIV transmission rates were 7.9% and 4% among breast and formula fed infants, respectively [33].

Venkatesh *et al.* compared rates of infant hospitalizations associated with infectious morbidity among infants whose mothers elected to breast or formula feed [34]. They documented HIV transmission rates of 18.4% and 13.2% among breast and formula fed infants, respectively by 3 months.

Outcomes

Growth

Kindra *et al.* found no difference in z-scores between breast and formula fed infants at 9 months of age [33].

Malnutrition

Mbori-Ngacha *et al.* defined malnutrition as a weight-for-height z-score value 2 SD below the mean. Becquet *et al.* defined malnutrition as an observation of either no change or a decrease in anthropometric measurements between study visits. Neither study found a statistically significant difference in malnutrition risk between breast and formula fed infants (RR = 0.63; 95% CI 0.36 to 1.12) and (HR = 1.35; 95% CI 0.93 to 2.0) [28] [32].

Respiratory tract infections

Mbori-Ngacha *et al.* do not describe how upper respiratory tract infections were defined [28]. The trial found no difference in rates of respiratory infections between breast and formula fed infants (HR = 1.00; 95% CI 0.90 to 1.11) [28].

Becquet *et al.* defined acute respiratory infection as cough, fever, and focal pulmonary findings [32]. Venkatesh *et al.* used WHO ICD-10 criteria to classify respiratory infections associated with hospitalizations [34]. The pooled estimate from these observational studies suggests a lower incidence of respiratory infections in breast than formula fed infants (HR = 0.65; 95% CI 0.41 to 1.00) [32] [34]. After adjusting for HIV status, breastfed infants were 40% less likely to develop respiratory infections (HR = 0.60; 95% CI 0.36 to 0.98) [32].

Diarrhoea

Diarrhoea was defined as passage of 3 or more watery stool per 24-hour period for at least 2 days. Mbori-Ngacha *et al.* found no difference over 2 years between breast and formula fed infants either when including both HIV-infected and HIV-uninfected infants (HR = 1.11; 95% CI 0.91 to 1.43) or in HIV-uninfected infants alone (HR = 1.11; 95% CI 0.83 to 1.43) [28]. Venkatesh *et al* reported similar findings (HR = 0.50 95% CI 0.15 to 1.70) as Mbori-Ngacha *et al.* Becquet *et al.* and Kindra *et al.* differ from Mbori-Ngacha *et al* and Venkatesh *et al.* Both studies found that breastfed infants were at lower risk for diarrhoea (RR = 0.31; 95% CI

0.13 to 0.74) [33], the risk was significantly lower for breastfed infants after adjusting for HIV status (HR = 0.74; 95% CI 0.57 to 0.97) [32].

2. Breastfeeding with extended ARV prophylaxis versus short-course ARV prophylaxis

A clinical adverse event is defined as any health-related reaction or effect experienced by a study participant. Serious clinical adverse events (SAEs) in infants were assessed as safety endpoints in studies comparing differing postnatal ARV prophylaxis. Five studies compared incidence of SAEs between infants exposed to different combinations of extended and short-course ARV prophylaxes during breastfeeding [9] [11] [26, 27] [30]. We use the term "extended ARV prophylaxis" to refer to interventions involving ARVs given for longer duration than the (short-course) peri-partum prophylaxes that were standard of care at the time the studies were conducted. Important assumptions were made for interventions in this comparison. First, Jamieson *et al.* and the Kesho Bora Study included maternal ARV interventions in their studies. Since mothers were breastfeeding while receiving the intervention, infants would be ingesting ARVs in breast milk. On this basis, we felt these interventions could reasonably be compared with ARV interventions administered directly to infants. This assumption is supported by findings of Shapiro *et al.*, that concentrations of NVP, lamivudine and ZDV in breast milk of HIV-infected women receiving HAART are similar to or higher than their serum concentrations, and that infant serum NVP concentrations were sufficient to inhibit HIV-1 replication [35]. Second, the studies by Jamieson *et al.* and Kumwenda *et al.* each tested two extended ARV regimens against a standard short-course regimen. We felt that the two extended ARV interventions in each study were sufficiently similar to combine the results for comparison with the short-course ARV group.

Four studies [9] [11] [27] [30] used standard Division of AIDS toxicity tables to grade severity of SAEs. One study [26] used the WHO International Classification of Disease (ICD-10) criteria. All five studies reported rates of SAEs without stratifying by infants' HIV status.

Coovadia *et al.* randomly assigned infants who had received 6 weeks of once-daily NVP to continue a once-daily NVP prophylaxis or placebo until 6 months of age [30]. Infants were followed-up until 18 months of age. At 12 months of age HIV transmission rates were 3.6% in the placebo group and 2.8% in the NVP group.

Gray *et al.* compared ZDV given to infants for the first six weeks of life to single dose (sd) NVP at delivery [26]. Cumulative HIV transmission rates at 12 weeks were 14.3% in the sd NVP group and 18.1% in ZDV group.

Jamieson *et al.* compared a control group of mothers given sd NVP during labour or at delivery, and mothers and infants receiving ZDV and lamivudine for 1 week, to two extended

ARV groups: postnatal either the mothers received HAART or infants received daily NVP until 28 weeks of age [11]. At 48 weeks of follow-up, HIV transmission rates were 7% in the control group and 4% in both extended ARV groups. We combined the extended ARV groups to allow pairwise comparison with the control group.

In the Kesho Bora Study [27] mothers received HAART until weaning or a maximum of 6.5 months post-partum (extended ARV group) or ZDV during pregnancy plus sd NVP at onset of labour (short-course ARV group) [27]. By 1 year of age 5.4% of infants in the extended ARV group became HIV-infected compared to 9.5% in short-course ARV group.

Kumwenda *et al.* compared sd NVP and ZDV given to infants for the first week of life (control group) to 14 weeks of NVP (extended NVP group) or 14 weeks of NVP plus ZDV (extended NVP plus ZDV group) [9]. At 9 months of age HIV transmission rates were 10.6%, 5.2% and 6.4% in the control, the extended NVP and the extended NVP plus ZDV groups, respectively. We combined the two extended ARV groups for pairwise comparison with the control group.

Outcomes

Growth faltering

The risk of growth faltering was 12% higher in infants on extended ARV prophylaxis than short-course ARV prophylaxis (RR = 1.12; 95% CI 0.83 to 1.50) [9] [11] [27] (Figure 3).
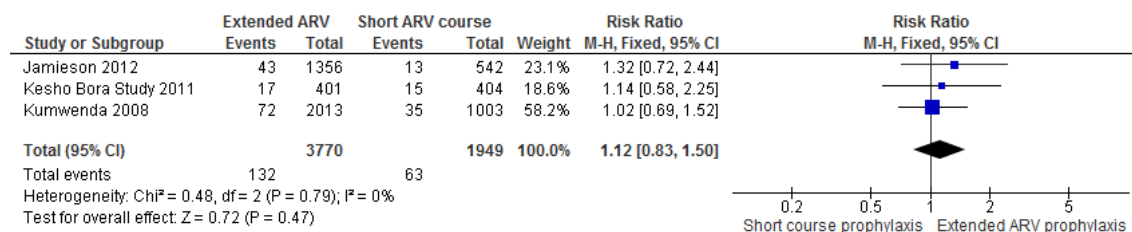
Study or Subgroup	Extended ARV Events	Total	Short ARV course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jamieson 2012	43	1356	13	542	23.1%	1.32 [0.72, 2.44]
Kesho Bora Study 2011	17	401	15	404	18.6%	1.14 [0.58, 2.25]
Kumwenda 2008	72	2013	35	1003	58.2%	1.02 [0.69, 1.52]
Total (95% CI)		**3770**		**1949**	**100.0%**	**1.12 [0.83, 1.50]**
Total events	132		63			

Heterogeneity: Chi² = 0.48, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

Risk Ratio M-H, Fixed, 95% CI
0.2 0.5 1 2 5
Short course prophylaxis   Extended ARV prophylaxis

Figure 3. Forest plot of breastfeeding with extended ARV prophylaxis vs. short-course ARV prophylaxis: Growth faltering

Pneumonia

The mean difference (MD) in incidence of pneumonia in the extended ARV prophylaxis group was -0.01 (95% CI -0.02 to -0.00) [9] [11] [26] [27] (Figure 4). The MD was -0.02 (95% CI -0.03 to -0.00) when we excluded the study with a high attrition rate. Risk of pneumonia was similar between the groups in Coovadia study [30].

Meningitis

There was no difference in meningitis incidence between extended and short-course ARV prophylaxis groups [9] [11].

Gastroenteritis

There was no difference in rates of gastroenteritis between extended and short-course ARV prophylaxis (MD = 0.01; 95% CI -0.01 to 0.02) [9] [11] [26, 27] (Figure 5). Coovadia *et al.* found no difference in risk of gastroenteritis between the two group (RR = 0.90; 95% CI 0.61 to 1.33) [30].

Sepsis

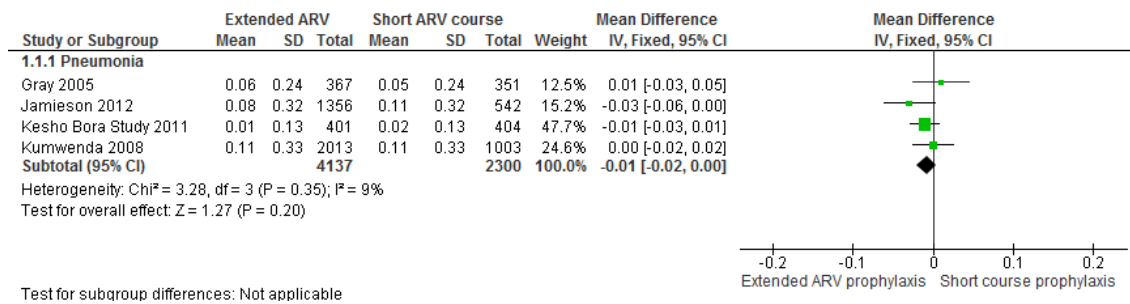Incidence of sepsis was similar between intervention groups [9].

Figure 4. Forest plot of breastfeeding with extended ARV prophylaxis vs. short-course ARV prophylaxis: Pneumonia
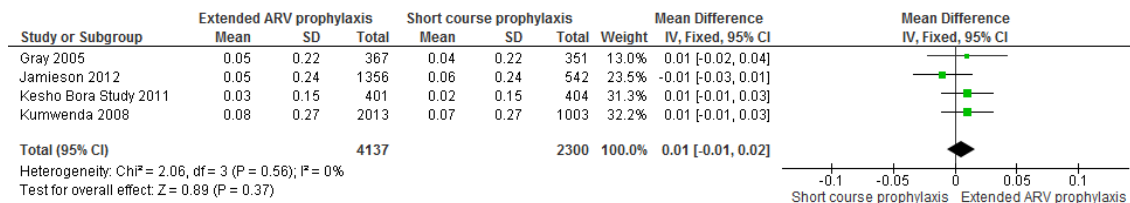

Figure 5. Forest plot of breastfeeding with extended ARV prophylaxis vs. short-course ARV prophylaxis: Gastroenteritis

3. Early breastfeeding cessation versus standard duration of breastfeeding

Two reports from a single RCT presented growth and diarrheal morbidity outcomes in HIV-exposed uninfected infants whose mothers were randomly assigned to stop breastfeeding at 4 months (intervention group) or to continue breastfeeding for as long as they wished, with

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the median duration being 16.2 months (control group) [23] [25]. HIV transmission rates were 21.4% and 25.8% in the intervention and control groups, respectively.

Outcomes

Growth

Weight-for-age z-scores at 2 years of age were similar between infants stopping breastfeeding early compared to continuing for a longer duration (MD = 0.12; 95% CI -0.10 to 0.34) [23].

Prolonged diarrhoea

Diarrhoea lasting for at least 7 days was defined as prolonged [25]. During the 7-24 months age period, the odds of having an episode of prolonged diarrhoea when breastfeeding was stopped early were almost twice that of breastfeeding for a longer duration (OR = 1.70; 95% CI 1.28 to 2.26).

4. Chemically or biologically acidified formula versus standard formula

Velaphi *et al.* compared infectious morbidity and growth between HIV-exposed uninfected infants receiving chemically or biologically acidified formula and those receiving standard formula for the first four months [31].

Infants were randomly assigned to four groups:

1. Non-acidified (standard) whey-adapted starter formula
2. Chemically acidified standard formula, where acidification was achieved through addition of L(+) lactic acid
3. Chemically acidified standard formula with *Bifidobacterium lactis* CNCM I-3446 added
4. Biologically acidified standard formula, where acidification was achieved through bacterial fermentation

We combined the two chemically acidified formula groups and the biologically acidified formula group for pairwise comparison with the standard formula group.

Outcomes

Growth

Z-scores were calculated based on growth charts from the Centre for Disease Control and Prevention (CDC) and were presented up to 4 months of age. Head circumference-for-age z-scores were significantly higher in infants who received acidified formulas compared to

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infants who received standard formula (MD = 0.31; 95% CI 0.15 to 0.48). The study found no significant differences in WLZ-scores (MD = 0.09; 95% CI-0.16 to 0.34, LAZ-scores (MD = 0.08; 95% CI -0.15 to 0.30) and WAZ-scores (MD = 0.18; 95% CI -0.05 to 0.41) between study groups.

Bronchopneumonia and gastroenteritis
The authors do not describe how infectious outcomes were defined. Incidence of bronchopneumonia (MD 0.12; 95% CI -0.03 to 0.27) and gastroenteritis (MD -0.07; 95% CI -0.17 to 0.02) between birth and 6 months of age were similar between infants on acidified formula and those on standard formula.

5. Concentrated formula versus Standard formula

Winter *et al.* assessed growth in HIV-exposed uninfected infants randomly assigned to receive either concentrated infant formula 87 kcal/100mL or standard formula 67 kcal/100mL [29].

Outcomes
Growth
Z-scores were calculated using the 2000 National Centre for Health Statistics paediatric growth references. Mean WAZ-scores was significantly higher for infants on concentrated formula than standard formula (MD = 0.12; 95% CI 0.04 to 0.20). We found no significant differences in WLZ-scores (MD = 0.11; 95% CI -0.01 to 0.23), LAZ-scores (MD = 0.03; 95% CI -0.06 to 0.12), and head-circumference-for-age z-scores (MD = -0.03; 95% CI -0.11 to 0.05).

6. Chemically acidified formula with or without prebiotics and nucleotides

Growth and infectious morbidity were compared in HIV-exposed, uninfected infants on chemically acidified formula alone and with prebiotics and nucleotides [24]. Infants were randomly assigned to three study groups and followed-up until 6 months of age:
1. Chemically acidified formula (control)
2. Chemically acidified formula with prebiotics (a blend of short-chain and long chain fructo-oligosaccharides)
3. Chemically acidified formula with prebiotics and nucleotides (a blend of cytidine, uridine, adenosine and guanosine monophosphates)
    Chemical acidification was achieved as in [31].

We combined outcomes from infants in groups 2 and 3 to allow pairwise comparisons with group 1.

Outcomes

Growth

Z-scores were calculated using the 2000 CDC growth charts. The primary study report presented summary data and corresponding 95% CIs in graph format. We estimated mean z-scores and SDs from the graphs.

Mean WAZ-scores (MD = 0.08; 95% CI -0.15 to 0.31) and LAZ-scores (MD = -0.14; 95% CI -0.39 to 0.1) were similar in all groups.

Table 2. Breastfeeding compared to formula feeding for HIV-exposed infants

Outcomes	Relative effect (95% CI)	Number of Participants (studies)	Quality of the evidence (GRADE)
Malnutrition RCT	**RR** 0.63 (0.36 to 1.12)	371 (1)	⊕⊕⊖⊖ **low**[*,ǂ]
Diarrhoea 'Cohort study, effect up to 2 years of age'	**HR** 0.74 (0.57 to 0.97)	557 (1)	⊕⊕⊕⊖ **moderate**[¶,*]
Diarrhoea 'Cohort study, effect up to 3 months of age'	**RR** 0.31 (0.13 to 0.74)	127 (1)	⊕⊖⊖⊖ **low**[¶,†]
Respiratory infections RCT	**HR** 1 (0.9 to 1.11)	371 (1)	⊕⊕⊖⊖ **low**[*,ǂ]
Respiratory infections Cohort	**HR** 0.60 (0.36 to 0.98)	557 (1)	⊕⊕⊕⊖ **moderate**[¶]
Diarrhoea RCT	**HR 1.11** (0.91 to 1.43)	371 (1)	⊕⊕⊖⊖ **low**[*,ǂ]

RR: Risk ratio; HR: Hazard ratio; [*]Study had some methodological limitations, [ǂ]Wide confidence interval and fails to exclude the null effect, [¶]Observed breastfeeding effect was considered clinically important, [†]Sample size was too small

Table 3. Breastfeeding with extended ARV compared to breastfeeding with short-course ARV prophylaxis for HIV-exposed infants

Outcomes	Illustrative comparative risks˟ (95% CI)		Relative effect (95% CI)	Number of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Breastfeeding with short course ARVs	**Breastfeeding with extended ARVs**			
Growth faltering	**Study population** **32 per 1000**	**36 per 1000** (27 to 48)	**RR 1.12** (0.83 to 1.5)	5719 (3)	⊕⊕⊕⊖ **moderate**[ᶦ,†]
Pneumonia	The average incidence of pneumonia ranged across control groups from **0.03 to 0.11**	The average incidence of pneumonia in the intervention groups was **0.01 lower** (0.02 lower to 0.00 higher)		6437 (4)	⊕⊕⊕⊖ **moderate**[ᶦ,*]
Meningitis	The average incidence of meningitis ranged across control groups from **0.0089 to 0.0147**	The average incidence of meningitis in the intervention groups was **0 higher** (0.01 lower to 0.00 higher)		4914 (2)	⊕⊕⊖⊖ **low**[¶,ᶦ]
Gastroenteritis	The average incidence of gastroenteritis ranged across control groups from **0.02 to 0.07**	The average incidence of gastroenteritis in the intervention groups was **0.01 higher** (0.01 lower to 0.02 higher)		6437 (4)	⊕⊕⊕⊖ **moderate**[ᶦ,†]

The assumed risk was based on the mean control group risk if there was one study included or on mean range in control group risk across studies, otherwise. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio. [ᶦ]There were too few studies to assess publication bias, [†]CI failures to exclude appreciable harm, [*]Point estimates vary widely, [¶]There were very few events

Discussion

Summary of main findings

We reviewed findings from 7 RCTs and 3 cohort studies evaluating effects of various postnatal interventions for prevention of MTCT of HIV.

 From our meta-analysis, breastfeeding appears to decrease the risk of respiratory infections by 35%, when infant feeding mode is self-selected and when not considering infant HIV status. However, this finding was not supported by the only RCT reporting on this comparison. There is moderate quality evidence that the risk of respiratory infection remains lower (by 40%) in breastfed infants through to 2 years of age, after adjusting for infant HIV status [32].

The evidence from this review is inconsistent on the effect of breast versus formula feeding on diarrhoeal morbidity. In three observational studies, breastfeeding significantly reduced risk of diarrheal morbidity in early life [33, 34], and, of diminished magnitude until the second birthday [32]. We graded this evidence of moderate quality. A randomised trial found no significant difference in diarrheal morbidity between breast- and formula fed infants up to 2 years of age [28]. This trial was not powered to test equivalence of diarrheal morbidity in the two arms. Therefore, it is important to avoid interpreting the lack of statistical significance as evidence of equivalent risk. Breastfeeding is expected to reduce diarrhoea incidence. There are a few possible explanations why this was not observed in this trial. HIV transmission was higher among breastfed than formula fed infants, probably obscuring the protective effect of breastfeeding. However, even when results from HIV-uninfected infants were analysed separately, no significant difference was found. A limitation of performing this type of sub-analysis is that the comparison groups are no longer "as randomized", therefore not necessarily comparable in baseline characteristics, thus possibly obscuring the true effect of breastfeeding. In our opinion, the most likely explanation is that as 30% of mothers assigned to the formula group had breastfed their infants [28], some protective effect of breast milk occurred in the formula group.

In the only RCT comparing breast versus formula feeding, the risk of malnutrition was 37% lower in breastfed infants. Though not statistically significant, the reduction in risk may be clinically important because the 95% CI includes strongly protective values at the lower limit and excludes values indicating appreciable harm from breastfeeding at the upper limit. Also, high HIV transmission rates in breastfed infants would be expected to attenuate any protective effect of breastfeeding, pulling the estimate towards the null. On the other hand, high rates of non-compliance in the formula-feeding group could be confounding this result. This evidence is judged of low quality. Further research comparing the nutritional outcomes of breast versus formula fed infants of HIV-infected mothers is warranted.

We found moderate quality evidence that breastfeeding with extended ARV prophylaxis is associated with fewer pneumonia episodes compared to breastfeeding with short-course ARV prophylaxis in HIV-exposed infants. The causal explanation remains unclear. If evidence of this association continues to accumulate, further investigation to explain the underlying biological mechanisms should be prioritised. However, high HIV transmission rates in infants on short-course ARV prophylaxis, especially in studies contributing substantial sample size to our meta-analysis [9] [27], could explain the higher incidence of pneumonia experienced by infants in this group.

Our meta-analysis shows a modestly increased risk for growth faltering among infants in the extended ARV group. This estimate has a wide CI, which includes the null effect. However, there is some evidence that infants exposed to ARV therapy *in utero,* compared to post-natal ZDV, have reduced growth up to 2 years of age (36) . Therefore, growth of infants exposed to post-natal ARVs should further studied.

We did not find the rates of any other SAEs to differ significantly between infants in the extended and short-course ARV prophylaxis groups. We do not believe that inadequate follow-up explains the lack of observed differences. In addition, with sample sizes of between 1898 and 5719 for different outcomes, it seems reasonable to conclude that extended ARV prophylaxis does not increase the risk for HIV-exposed infants to experience non-HIV infections outcomes compared to short-course ARV prophylaxis.

Conclusions

Implications for practice

Breastfeeding may reduce the risk of diarrheal morbidity, respiratory tract infections and malnutrition compared to formula feeding in HIV-exposed infants. Extended ARV prophylaxis and formula feeding effectively reduce or prevent late postnatal transmission of HIV infection (19). The magnitude of absolute benefit of breastfeeding combined with extended ARV prophylaxis may be sufficient to improve survival of children.

The benefits of breastfeeding with extended ARV prophylaxis must be weighed against the risk of HIV transmission through breast milk when making decisions about feeding HIV-exposed infants. Baseline risks, such as maternal viral load, safety of ARVs and sustained adherence should also influence decisions. Uptake of exclusive breastfeeding is reportedly poor in most African settings [37, 38]. Sub-optimal infant feeding practices are likely to modify the effectiveness of breastfeeding with ARV prophylaxis, especially in normal practice settings. Continuous evaluation of these interventions to determine whether their effectiveness remains clinically important should be a priority as these interventions are introduced in to clinical practice.

Implication for research

Large prospective cohort studies with sufficient length of follow-up are justified to investigate the effectiveness of postnatal interventions for PMTCT of HIV in normal practice settings. The studies should include infectious morbidity and infant growth as primary outcomes. Effects of specific infant formulas on growth require further evaluation.

Competing interests

The authors declare that they have no competing interests

Disclaimer
The views expressed in this article are those of the authors and do not necessarily reflect the view of the funders.

Authors' contributions

MZ: Contributed in conception and design of review, screened search results, data extraction, analysis and interpretation, and writing of the manuscript.

GDM: Assisted in designing the review protocol, screened search results, extracted data, rated evidence, and assisted with analysis and interpretation, and writing of the manuscript.

LT: Revised manuscript, gave input on statistical analysis and interpretation.

ME: Contributed in conception of review, edited the manuscript and gave input on interpretation.

MC: Contributed in conception and design of review, edited the manuscript and gave input on interpretation.

All authors have read and approved the final manuscript.

Additional files

Additional file 1: Search strategies
Search strategies used in each database (PDF)

Additional file 2: Characteristics of included studies

Study methods, eligibility criteria, study outcomes, interventions assessed and risk of bias assessment (PDF)

Additional file 3: Excluded studies

List of excluded studies and reasons for exclusion (PDF)

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Appendix 2:

Chart Extraction guide

- Section A (History) data to be collected as close to admission as possible. Any unrecorded information ask mom directly if she is available.
- Section B-E data to be collected at end of admission.
- Infants length and TB culture results may need to be followed up at a later date.

General Admission Details

1. Study ID number: or study sticker can be placed here
2. Hospital: circle appropriate hospital or specify if not listed. Indicate the hospital at first presentation.
3. Date of admission: all dates with months in letters e.g. Jan, Feb, Mar
4. Date of final discharge home: if referred to another hospital, this is the final date of discharge home, not date of transfer from presenting hospital to referral hospital
5. Problem list: taken from the doctor's daily notes and the discharge summary; DO NOT include HIV exposure in the list; can be more than 6 if applicable
6. Referral to another hospital: indicate which hospital
7. ICU care: could be ICU at secondary or tertiary hospital

A. History on Admission

Systemic Enquiry:
1. Cough < 14/7: ok if duration of cough not specified but rest of hx < 14/7
2. Cough ≥ 14/7: ok if has received broad spectrum antibiotics and not responded to them with a vague duration or duration >9 but < 14/7
3. Fever < 14/7: ok if duration of fever not specified but rest of hx < 14/7
4. Coryza or rhinitis: "runny nose" ok
5. Difficulty breathing: "short of breath", "fast breathing" ok
6. Apnea episodes: "stopped breathing", "turned blue" ok
7. Vomiting everything: "persistent vomiting" ok, vomiting all source of nutrition i.e. all milk < 6 months, all milk and solids > 6 months ok
8. Liquid stools: more unformed than usual, with increased number, "runny stools", "loose stools", "diarrhea stools", "watery stools" ok
    a. <14/7 ok if duration of diarrhea not specified but rest of hx < 14/7
9. Bloody stools: "any blood in stools", "dysentery" ok
10. Convulsions: "seizures" ok
11. Fatigue or reduced playfulness: "less active than usual", "more sleepy than usual" ok
12. Weight: to inspect from RTHB if available; if RTHB not available then take from admission notes

Past Medical History:
This section should be completed from hospital notes and MIHS source document of study doctors assessment
13. Known congenital abnormality: includes genetic syndromes e.g. Trisomy 21 (Down Synd), Fetal Alcohol Spectrum Disorder; specify congenital abnormality
14. Known chronic acquired disease: includes chronic conditions that are not congenital e.g. cerebral palsy, nephrotic syndrome, seborrheic dermatitis or atopic eczema
15. Known TB contact: an adult who has had pulmonary tuberculosis in the last 12 months and who lives in same household as child or someone with whom the child is in contact for long periods

B. Physical Examination

- Yes, < 48hrs = sign was present but for less than 48 hrs

- Yes, $\geq$ 48 hrs = sign was present for 48 hrs or more (consider sign to be present $\geq$ 48 hours if noted on two consecutive daily morning rounds notes)
- No = sign was never present
- Unknown = sign was not reported on in hospital notes
- 1-5 below will be recorded in nursing notes

1. Weight: recorded in casualty observations or first ward observations on admission
2. Length: may not be well recorded; if length unknown extrapolate from length at study visit on either side of admission
3. MUAC: unlikely to be present, but record if is
4. Temperature: from nursing observation chart for entire admission
5. Tachypnea for age: 0-2 months > 60bpm; >2-12 months > 50bpm; from nursing observation chart for entire admission
6. Acutely unwell: "shocked" ok
7. Irritable: only if noted on examination and persistently irritable $\geq$ 48 hours
8. Cervical lymph node mass: ok if just noted to be > 2x2cm or "large"
9. Conjunctivitis: includes eye discharge
10. Skin pinch 1-2sec: capillary refill time (CRT) 1-2 sec ok
11. Skin pinch > 2 sec: CRT > 2 sec ok
12. Unable to eat orally: only important if oral ulceration present
13. Diffuse vesicular rash: "blistery rash" ok
14. Visible ear discharge: "pus in ear canal" ok
15. Inflamed tympanic membrane: "red", "hyperemic" ok
16. Lower chest wall indrawing, recession: retractions ok
17. Engagement of abdominal muscles on expiration: "prolonged expiration" ok
18. Liver ptosis: "liver pushed down" ok
19. Stridor on inspiration only: Grade 1 stridor/croup ok
20. Stridor on inspiration and expiration: Grade 2 or > stridor/croup ok
21. Neck stiffness: "meningism" ok
22. Spinal angulation: "spinal deformity" ok

C. Investigations

Laboratory Investigations (HIV Test & TB Microbiology)
1. Done-yes: means yes investigation done *during admission*
2. Done-no: means no investigation not done *during admission*
3. Result: positive or negative i.e. mTB culture positive, mTB culture negative, HIV PCR positive, HIV PCR negative

Chest X-Ray
1. Done-yes: means yes investigation done *during admission*
2. Done-no: means no investigation not done *during admission*
3. Result: next to each of the statements "Suggestive of PTB" or "Bilateral Hyperinflation", indicate *positive* if doctor's notes contained such an affirmative statement with regards to PTB or hyperinflation or *negative* if doctor's notes did not contain such an affirmative statement or contained a negative statement with regards to PTB or hyperinflation.

D. Treated For

Only record if treatment initiated for the condition during this admission.

1. For all TB diagnoses: if listed on discharge summary and discharged on TB medication (RIF, INH, PZA +/- ETH or EMB)
2. Extrapulmonary TB: specify type e.g. TB meningitis, TB pericarditis, abdominal TB
3. Meningitis: treated for viral or bacterial meningitis whether confirmed on culture or not; don not include TB meningitis here
4. Bacterial septicemia: > 28 days old; only blood culture positive and specify organism
5. Presumed septicemia: or "presumed sepsis"; > 28 days old; treated for bacterial sepsis but blood culture negative or not done
6. Urinary tract sepsis: if > 2 organisms cultured on urine sample, unlikely to be from a sterile urine specimen (discuss with Amy)
7. Neonatal sepsis without meningitis: only ≤ 28 days; "presumed neonatal sepsis" ok
8. Neonatal sepsis with meningitis: only ≤ 28 days; with abnormal CSF
9. Other pediatrician/neonatologist diagnosed congenital infection: specify the infection

Appendix 3:

Infectious cause hospitalization classification and grading definitions

A. Respiratory Tract Infections

Criteria for pneumonia and tuberculosis can be fulfilled concurrently for the same event

Criteria for pneumonia and bronchiolitis cannot be fulfilled concurrently for the same event

1. Pneumonia

- History of cough or difficulty breathing

PLUS

- Tachypnea for age (on presentation/admission)

  [0-2 months > 60bpm, 2-12 months > 50bpm]

OR

- Nasal prong or nasal cannula O_2 required for transfer to hospital

WITHOUT

- Wheeze

Severe

At least 1 of the following

- ✓ Lower chest wall indrawing or nasal ⎤ flaring
- ✓ Not able to drink or breastfeed
- ✓ Vomiting everything   * General Danger Signs
- ✓ Convulsions during this illness
- ✓ Lethargic or unconscious ⎦
- ✓ O_2 saturation $\leq$ 92% on room air measured by pulse oximeter
- ✓ NPO_2 required to keep O_2 saturation > 92 % measured by pulse oximeter

Mild-moderate

No features of severe pneumonia

2. Tuberculosis

- Started on TB treatment in hospital (none of below criteria necessary)

OR

- A close TB contact (an adult who has had PTB in last 12 months, who lives in the same household as child or someone with whom the child is in contact for long periods)

PLUS 2 or more of the following

- Persistent non-remitting cough or wheeze for > 2 weeks that has not responded to broad spectrum antibiotics for community acquired pneumonia
- Documented loss of weight, no weight gain, or unsatisfactory weight gain (i.e. not following own curve or crossing centiles downwards)
- Fatigue or reduced playfulness
- Persistent fever > 2 weeks
- Painless enlarged mass of matted cervical lymph nodes (> 2x2 cm), without visible local cause on scalp or response to oral antibiotics

AND/OR

- Abnormal chest X-ray suggestive of PTB (enlarged hilar lymph nodes; airway compression; lung parenchymal disease; miliary dissemination)

OR

- Bacteriological confirmation of TB on sputum, gastric aspirate or lymph node fine needle aspiration biopsy

Severe

At least 1 of the following

- ✓ Severe respiratory distress – tachypnea for age PLUS at least 1 of lower chest wall indrawing or O_2 required
- ✓ Wheezing (low pitched monophonic) not responding to bronchodilator
- ✓ Headache, neck stiffness, drowsiness, irritability, convulsions
- ✓ Hepatosplenomegaly (age defined)
- ✓ Peripheral oedema
- ✓ Distended abdomen with or without ascites
- ✓ Angulation of the spine/gibbus

OR

Hospital diagnosed extrapulmonary or miliary TB

Mild-moderate

No features of severe tuberculosis

3. Bronchiolitis

- History of cough or difficulty breathing

PLUS 1 of the following

- Wheeze on history or physical exam

- Evidence of hyperinflation on physical exam (liver ptosis or reduced cardiac dullness on percussion)
- Evidence of hyperinflation on chest X-ray (> 8 posterior ribs above the diaphragm)

Severe

At least 1 of the following

- ✓ Tachypnea for age [0-2 months > 60bpm, 2-12 months > 50bpm]
- ✓ Lower chest wall indrawing, nasal flaring or engagement of abdominal muscles on expiration
- ✓ Not able to drink or breastfeed
- ✓ Vomiting everything
- ✓ Convulsions during this illness
- ✓ Apnoea on history or witnessed
- ✓ Lethargic or unconscious
- ✓ O_2 saturation $\leq$ 92% on room air measured by pulse oximeter
- ✓ NPO_2 required to keep O_2 saturation > 92 % measured by pulse oximeter

Mild-moderate if

No features of severe bronchiolitis

B. Diarrhoea

1. Acute Diarrhoea

- Liquid stools (more unformed than usual) with increased number of stools < 14 days

Severe

At least 2 of the following

- ✓ Lethargic or unconscious
- ✓ Sunken eyes
- ✓ Not able to drink or drinking poorly
- ✓ Skin pinch takes > 2 seconds to return to normal

Mild-moderate

No signs of severe

2. Persistent Diarrhoea

- Liquid stools (more unformed than usual) with increased number of stools $\geq$ 14 days

Severe

At least 2 of the following (any dehydration)

- ✓ Lethargic or unconscious
- ✓ Restless or irritable
- ✓ Sunken eyes
- ✓ Not able to drink, drinking poorly, drinking eagerly, thirsty
- ✓ Skin pinch takes > 1 second to return to normal

OR

- ✓ Any loss of weight

Mild-moderate

No visible dehydration or weight loss

3. Dysentery

- • Any blood in the stool

Severe

At least 1 of the following

- ✓ Age < 12 months
- ✓ Any dehydration present

Mild-moderate

No features of severe dysentery

C. Skin and mucocutaneous infections

1. Measles

- • Fever AND diffuse maculopapular rash

PLUS 1 of

- • Cough, coryza or conjunctivitis

Severe

At least 1 of the following

- ✓ Pneumonia (as previously defined)
- ✓ LTB (as previously defined)
- ✓ Diarrhoea (as previously defined)
- ✓ Any general danger signs*

Mild-moderate

No features of severe measles

2. Varicella Zoster

- • Fever AND diffuse vesicular rash

Severe

At least 1 of the following

- ✓ Pneumonia (as previously defined)
- ✓ LTB (as previously defined)
- ✓ Any general danger sign*

Mild-moderate

No features of severe varicella zoster

3. Non-specific viral exanthema

- Fever AND rash

AND

- Doesn't meet criteria for measles or varicella zoster

Severe

Presence of any general danger sign*

Mild-moderate

No features of severe viral exanthem

4. Stomatitis

- Erythema AND ulceration of oral mucosa (lips, gingiva or tongue)

Severe

At least 1 of

- ✓ Stridor
- ✓ Unable to eat orally, requiring nasogastric, orogastric or intravenous fluids

Mild-moderate

No features of severe stomatitis

5. Bacterial Skin Infection

At least 1 of

- Impetigo (diffuse pustular eruption)
- Abscess

Severe

Presence of any general danger sign*

Mild-moderate

No features of severe bacterial skin infection

D. Central nervous system infections

<u>1. Meningitis</u>

- Hospital diagnosis of meningitis based on clinical features and abnormal cerebrospinal fluid

E. Invasive bacterial infections

Hospital diagnosis of any one of the following:

1. Neonatal sepsis – diagnosed before 28 days of life
    a. confirmed – blood culture positive
    b. presumed – no positive blood culture, but treated for neonatal sepsis with a minimum duration of admission of 7 days
2. Postneonatal sepsis – diagnosed after 28 days of life
    a. confirmed - blood culture positive
    b. presumed – no positive blood culture, but treated for presumed bacterial sepsis with a minimum duration of admission of 7 days
3. Urinary tract sepsis – sterile urine culture positive
4. Septic arthritis – specialist diagnosis
5. Osteomyelitis – specialist diagnosis
6. Pyomyositis – specialist diagnosis

F. Congenital Infections

Hospital diagnosis of any one of the following
1. Congenital tuberculosis
2. Congenital syphilis
3. Congenital CMV
4. Neonatal Herpes Simplex Virus infection
5. Other paediatrician diagnosed congenital infection

Appendix 4:

Factors Associated With HIV-infected Mothers' Perceptions Of And Reactions To, Infant Feeding Choices In South Africa

Tuesday, 19 August 2014

Exhibit hall (Dena'ina Center)

Moleen Zunza, MA , Stellenbosch University, Stellenbosch, South Africa

Monika Esser, MD , Stellenbosch University, Tygerberg, South Africa

Julie. A Bettinger, PhD , University of British Columbia, Vancouver, BC, Canada

Mark.F Cotton, PhD , Stellenbosch University, Tygerberg, South Africa

INTRODUCTION: As Prevention of mother-to-child transmission transitions towards universal combination antiretroviral therapy (cART), the incidence of breastfeeding is increasing and formula feeding decreasing for HIV-exposed infants in the Western Cape province of South Africa. In a prospective cohort study (the Mother-Infant Health Study) we are assessing infant feeding practices in HIV exposed infants. This sub-study assessed HIV infected mothers' perceptions of and reactions to feeding their infants. The aim of this study was to capture, from a phenomenological perspective, a socially constructed view of HIV infected mothers' lived experiences regarding feeding their infants.

METHODS: Through application of Interactive Qualitative Analysis, two separate focus group discussions, a) breastfeeding mothers (n = 7) and b) formula feeding mothers (n =8) were conducted to determine factors associated with their feeding experiences. The focus group discussions were conducted in November 2013. Mothers reflected on their thoughts, beliefs, and experiences regarding feeding their infants. In depth individual interviews (n = 24) based on focus group responses were then conducted to explore the personal meaning, relevance, and life history examples of the themes with the mother.

RESULTS: Preliminary findings revealed that the main factors comprising experiences of breastfeeding HIV positive mothers were: advice on breastfeeding, reasons for wanting to breastfeed, choosing a feeding option that could make a baby sick (HIV infected), discouragement of breastfeeding, and challenges of breastfeeding. Main factors that described HIV positive formula feeding mothers experiences were: advice on formula feeding, consideration of baby's health, social expectations, disclosure of HIV status, making decisions about their own situation and fear of HIV transmission to their infant.

CONCLUSIONS: Breastfeeding and formula feeding HIV positive mothers had different feeding experiences. Factors that describe HIV positive mothers' infant feeding experiences should be explored on how they relate to each other to understand the meaning mothers attach to their feeding experiences.

Available from: https://wce.confex.com/wce/2014/webprogram/Paper3392.html

Appendix 5

Infant feeding choices and effects on infant morbidity in PMTCT programs transitioning to "option b+" in Western Cape, South Africa: The mother infant health study

Moleen Zunza ,Mark F. Cotton, , Monika Esser

Introduction Since the discovery of HIV transmission through breast milk more than 30 years ago, guidelines for feeding infants born to HIV-infected women have been changing. Despite the current recommendations for HIV-infected women to breastfeed with combination antiretroviral treatment, there are limited data on morbidity and growth of infants who are cared for in normal practice settings. The objective of this study was to determine the effect of infant feeding on morbidity and growth among predominantly breastfed and formula-fed HIV-exposed over a 12 months period. MethodsWe performed a longitudinal cohort study between July 2012 and December 2013 at Kraaifontein Midwife Obstetric Unit.

Results One hundred eighty three HIV-exposed uninfected infants were included in the analysis. Of these, 80 (44%) were in the breastfeeding group and 103 (56%) were in the formula feeding group at baseline. The follow-up rate was 28 of 80 (35%) in the breastfeeding group and 47 of 103 (46%) in the formula feeding group. The median (range) duration of breastfeeding was 1.93 (0.43 to 12.06) months and that of formula feeding was 8.94 (0.46 to 12.75) months. There were 37 infection related hospitalizations, twelve of these occurred among predominantly breastfed infants and 25 occurred among predominantly formula fed infants. The unadjusted and adjusted odd ratio of hospitalization due to major infectious morbidity among formula fed children compared to those who were breastfed was 1.53 (0.56 to 4.18) and 1.10 (95% CI: 0.38 to 3.20). We found no differences in weight-for-age, length-for-age and weight-for-length z -score between predominantly breastfed and predominantly formula fed infants.

Conclusion Women who chose to breastfeed quickly switched to formula feeding. Infection related hospitalizations tended to be fewer among predominantly breastfed infants. PMTCT programs need to adopt strategies that improve adherence to prolonged breastfeeding for the benefits to be realized at population level.

Available from:
http://www.sun.ac.za/english/faculty/healthsciences/aad/Documents/Programme_59th%20Annual%20Academic%20Day.pdf