EXCLUSIVE BREASTFEEDING IN THE PREVENTION OF HIV-1 TRANSMISSION FROM MOTHER TO CHILD: A SYSTEMATIC REVIEW

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Thesis presented in partial fulfilment of the requirements for the degree of Masters of Nursing Science in the Faculty of Health Sciences at the University of Stellenbosch

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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ABSTRACT

HIV infection poses a major obstacle in breastfeeding as it represents the most common way by which children acquire HIV. Exclusive breastfeeding has been discovered as the most effective intervention in preventing mother-to-child transmission of HIV, mortality and promotion of HIV free survival.

The main objective was to evaluate the evidence on the effectiveness of exclusive breastfeeding versus formula feeding and/ or mixed feeding in the prevention of HIV-1 transmission from mother to child.

To identify the studies, an electronic search was conducted using PUBMED/MEDLINE, CINAHL, CENTRAL and EMBASE databases. Electronic journals, which include the Southern African Journal of HIV medicine (SAJHIV), HIV Medicine Journal and American Journal of Public Health, were also accessed. Manual searches were carried out. In addition, relevant experts were contacted in order to locate more data. There were no limitations with regards to date and language.

The review considered studies on infants who were vertically HIV-1 exposed (mother HIV positive during pregnancy, birth and breastfeeding). These infants were exclusively breastfed for six months with administration of antiretroviral prophylaxis and were compared to infants exclusively formula fed. The outcomes measured were vertically acquired HIV infection; mortality and HIV free survival up to 24 months of age.

Two reviewers independently selected articles which met the inclusion criteria. They independently extracted the data using a data extraction tool. Disagreements were solved by discussion. Data was then meta-analysed using Rev Man 5.1.0.

Methodological quality of each trial was assessed by the reviewers using the Cochrane assessment tool for risk of bias.

Two randomised clinical trials and one intervention cohort study (n=2112 infants) comparing exclusive breastfeeding with exclusive formula feeding were included. HIV infection was associated with exclusive breastfeeding as compared with exclusive formula feeding (Risk ratio 1.67, 95% CI 1.26 to 2.23, p=0.0005). Exclusive formula feeding was associated with high mortality from infections (Risk ratio of 0.67 95% CI 0.43 to 0.83, p=0.002 Chi^2= 1.30, p=0.52, I^2=0%). There were no statistically significant differences in HIV free survival between exclusive breastfeeding and exclusive formula feeding as measured by trialists at 9,

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18 and 24 months (Risk ratio 1.19, 95% CI, 0.92 to 1.54, p=0.19, Chi^2= 3.15, p=0.21, I^2=36 % 3 studies, 1012 infants). None of the studies included reported on mixed feeding.

Complete avoidance of breastfeeding is effective in preventing mother-to-child transmission of HIV. HIV infection during breastfeeding might be an indicator of mixed feeding and poor adherence. Formula feeding is only applicable in settings where formula milk is accessible, feasible, acceptable, safe and sustainable (AFASS) because formula feeding carries a high risk of mortality from causes other than HIV. If the AFASS criteria cannot be met, mothers should be encouraged to exclusively breastfeed and ensure that their infants completely adhere to the antiretroviral prophylaxis because they decrease the rate of vertical HIV-1 transmission.

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OPSOMMING

MIV besmetting veroorsaak ‘n groot struikelblok vir borsvoeding, omdat dit die mees algemene manier is waarop babas met MIV besmet word. Eklusiewe borsvoeding is as die mees effektiewe intervensie ontdek in die voorkoming van moeder na kind oordrag van MIV, morbiditeit en die bevordering van MIV vrye oorlewing.

Die hoofdoelwit is om die effektiwiteit van eksklusiewe borsvoeding teenoor formule-voeding en of gemengde voeding in die voorkoming van MIV oordrag van moeder na kind te evalueer.

Elektroniese navorsing is gedoen deur gebruik te maak van PUBMED/MEDLINE, CINAHL, CENTRAL en EMBASE databasisse. Elektroniese joernale wat die Southern African Journal of HIV medicine (SAJHIV), HIV Medicine Journal and American Journal of Public Health insluit, is ook gebruik. Handnavorsing is ook gedoen, asook relevante data van kenners op die gebied, is verkry. Geen beperking is geplaas op taal of tyd nie.

Studies op babas wat blootgestel is aan die MIV-1 (moeder MIV positief gedurende swangerskap en borsvoeding) is in die oorsig oorweeg. Hierdie babas is eksklusief vir 6 maande gerborsvoed, met of sonder anti-retrovirale behandeling, en is vergelyk met eksklusiewe formule-voeding. Die resultaat was dat almal tot op 24 maande gemeet is aan MIV besmetting, mortaliteit en MIV vrye oorlewing.

Twee resensente het onafhanklik artikels geselekteer wat aan die ingeslote kriteria voldoen het. Hulle het onafhanklik data geselekteer deur van ’n selekteringsinstrument gebruik te maak. Misverstande is deur besprekings opgelos. Data was daarna gemeet en gemeta-analiseer deur Rev Man 5.1.0.

Die metadologiese kwaliteit van elk proeflopie is geassesseer deur die resensente wat gebruik gemaak het van die Cochrane evalueringsinstrument om die risiko van onewewigtigheid uit te skakel.

Twee ewekansige kliniese proewe en een intervensie kohort studie (n = 2112 babas) wat eksklusiewe borsvoeding vergelyk met 'n eksklusiewe formule-voeding is ingesluit. MIV-infeksie wat verband hou met 'n eksklusiewe borsvoeding is vergelyk met eksklusiewe formule-voeding (risiko verhouding van 1.67, 95% CI 1.26 tot 2,23, p=0.0005). Eksklusiewe formule-voeding hou verband met 'n hoë mortaliteit van infeksies met ’n risiko verhouding van 0.67, 95% CI 0.43 tot 0.83, p = 0.52, Chi ² = 1.30, p = 0.52, I ² = 0%. Daar is geen

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statisties beduidende verskille in MIV-vrye oorlewing tussen eksklusiewe borsvoeding en eksklusiewe formule-voeding nie wat deur die proefnemers gemeet is op 9, 18 en 24 maande (risiko verhouding 1.19, 95% CI, 0.92 tot 1.54, p = 0,19, Chi ² = 3,15, p = 0.21, I ² = 36% 3 studies, 1012 babas). Nie een van die ingeslote studies het verslag gedoen oor gemengde voeding nie.

Algehele vermyding van borsvoeding is effektief in die voorkoming van Moeder na Kind oordrag van MIV. MIV-infeksie gedurende borsvoeding mag ’n aanduiding van gemengde voeding en swak nakoming wees. Formule voeding is alleenlik van toepassing in situasies waar formule-melk toeganklik, uitvoerbaar, veilig en volhoubaar is, want formule-voeding dra ’n hoë risiko van mortaliteit weens ander oorsake buiten MIV. Indien daar nie aan hierdie kriteria voldoen kan word nie, behoort moeders aangemoedig te word om eksklusief te borsvoed en seker te maak dat hulle babas die antiretrovirale profilaksie getrou neem, want dit verlaag die koers van vertikale MIV-1 oordrag.

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LIST OF ABBREVIATIONS

AFASS	Affordable, Feasible, Accessible, Sustainable, Safe
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral
CENTRAL	Cochrane Central Register of Controlled trials
CINAHL	Cumulative Index of Nursing and Allied Health Literature
EBF	Exclusive Breastfeeding
EFF	Exclusive Formula-feeding
ELISA	Enzyme Linked Polymerase Chain Reaction
EMBASE	Excerpta Medica Database
HAART	Highly Active Antiretroviral therapy
HIV	Human Immune Deficiency virus
MEDLINE	Medical Literature Analysis and Retrieval system Online
MTCT	Mother-to-child-transmission
PCR	Polymerase Chain reaction
PMTCT	Prevention of mother-to-child
RV	Retroviral
SANAC	South African National AIDS Council
UNICEF	United Nations Children's Fund
WHO	World Health Organisation

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CHAPTER 1

SCIENTIFIC FOUNDATION OF THE STUDY

1.1 INTRODUCTION

BACKGROUND: DESCRIPTION OF THE CONDITION AND INTERVENTION

Human immune-deficiency virus (HIV), the causative virus of Aquired Immune Deficiency Syndrome (AIDS), is transmitted in various ways to an infant. Vertical or mother-to-child transmission of HIV can occur transplacentally in utero, at the time of delivery or through breastfeeding (Cronje & Grobbler, 2003:428). According to Nolte (2007:359), a woman may acquire HIV during sexual intercourse with an infected partner, through sharing of infected objects or during blood transfusion with HIV infected blood.

During the past decades, breastfeeding has been encouraged to improve both maternal and child health. Holmes and Salvage (2007:1065) indicated immediate and long term benefits of breastfeeding, which is a cost effective intervention for child survival which could prevent 13-15% of child deaths in low income countries. Breastfeeding protects against common infections such as diarrhoea, pneumonia, neonatal sepsis and otitis media (Newell, 2004:5). A study conducted in Brazil found that infants who were not breastfed were 17 times at higher risk of hospital admission (OR 16.7, 95% CI 7.7-36) (Newell, 2004:5). According to Horvath, Madi, Kennedy, Rutherford and Read (2010:4), the epidermal growth factor in the colostrum helps to make the gastrointestinal tract less permeable to viral infection.

Without any specific interventions, HIV transmission via breastfeeding accounts for an estimated 24-44% of infant infections (Lehman, Chung, John-Stewart, Kinuthia & Overaugh, 2008:2). According to Holmes and Salvage (2007:1065), the joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that over 300 000 children are infected with HIV through breastfeeding every year. Despite the conflicting issue of breastfeeding being a risk factor for HIV infection in HIV-1 exposed infants and breastfeeding being important in the promotion of growth and protection against common infections, exclusive breastfeeding will reduce the chances of HIV transmission as opposed to mixed feeding. (Newell, 2004:5). Exclusive breastfeeding implies that an infant receives only breast milk, and no other liquids or solids, not even water, with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines (Newell, 2004:1).

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Mixed feeding disturbs the lining or causes trauma to the gastrointestinal tract of the infant, hence the risk of mother-to-child transmission of HIV is higher (Fraser, Cooper & Nolte, 2006:366). According to the Department of Health in the Republic of South Africa (2008:115), mixed feeding carries the highest risk of HIV transmission and should be discouraged.

Replacement feeding with formula feeding carries a higher infant mortality risk (Thior, Shapiro, Smeaton, Lockman, Rossenkhan, et al., 2009:1). To make breastfeeding safe, breast milk pasteurization, a hot water bath and microbicidal treatment with alkyl sulphates have been proposed (Thior et al., 2006:794).

Currently, HIV exposed infants are given doses of antiretroviral medication. Such prophylaxis is designed to protect the uninfected infant while exposed to the HI-virus through breastfeeding. Prophylactic antiretroviral regimes are taken during pregnancy, intrapartum and postnatally by the mother, as well as by the infant postpartum. In places of adequate infrastructure, the World Health Organisation currently recommends a combination of these regimens (lamuvidine, zidovudine and nevirapine) (WHO, 2009: 9). In developing countries a single daily dose of nevirapine remains to be widely used and has been proven to reduce HIV transmission via breast milk during the early postpartum period when the majority of breast milk transmission occurs (Lehman et al., 2008:2).

Several studies have been conducted to prove the effectiveness of exclusive breastfeeding in HIV exposed infants. In Botswana, Thior et al., (2006:1-13), compared exclusive breastfeeding plus infant zidovudine prophylaxis for 6 months with formula feeding, plus infant zidovudine for one month. The results of this randomised controlled study reported comparable rates of HIV-free survival at 18 months in both interventions. Formula feeding had a higher risk of high morbidity and mortality rates but breastfeeding with zidovudine prophylaxis had a higher risk of HIV transmission at 7 months. In a study carried out in Kwazulu-Natal in South Africa, exclusively breastfed infants carried a significantly lower risk of transmission of HIV than all types of mixed feeding. Those who received breastmilk and solids were eleven times at risk of becoming HIV infected, while those on breastmilk and formula feeds were twice at risk (Coovadia, Rolling, Bland, Little, Coutsoundis et al., 2007:1112).

In a systematic review conducted by Horvath et al., (2010:17), six randomised clinical trials and one intervention cohort study were included and they concluded that complete avoidance of breastfeeding is efficacious in preventing mother-to-child transmission of HIV.

Furthermore, if breastfeeding is initiated, the two interventions that are efficacious in preventing transmission are exclusive breastfeeding and extended antiretroviral prophylaxis.

1.2 PROBLEM STATEMENT

The effectiveness of exclusive breastfeeding among HIV exposed infants is still unclear. There are numerous controversial and ethical issues surrounding this intervention. Through postnatal experience, some health care professionals do not approve of exclusive breastfeeding in HIV cases due to reported high transmission rates; as a result they fail to reinforce exclusive breastfeeding when it is applicable. Mothers are exposed to the HIV stigma if they do not breastfeed, as there is an assumption that the mother is HIV positive, while in other cases women suffer the abuse of family members, especially from male family members. Most women lack information on the effectiveness of exclusive breastfeeding in HIV exposed infants.

1.3 HOW EXCLUSIVE BREASTFEEDING MIGHT WORK

Exclusive breastfeeding is considered the best feeding option in poorly resourced communities where formula feeding is not feasible, unacceptable, unsafe, not sustainable and unaffordable. An extensive literature search has shown that exclusive breastfeeding reduces other significant risks, such as increased diarrhoea and pneumonia morbidity and mortality (Thior et al., 2006:1-13: Newell 2004:5).

Exclusive breastfeeding with antiretroviral prophylaxis is associated with less than 5% HIV transmission. In the MITRA Plus trial from Tanzania, ART and breastfeeding was associated with a cumulative transmission at six months of only 5.0% (less than 1% had been infected during the period of breastfeeding) (Kilewo, Karlsson, Ngarina, Massawe, Lyamuya et al., 2008:1). The AMATA study in Rwanda, found that only one out of 174 (0.6%) breastfeeding women on maternal Highly Active Antiretroviral Therapy transmitted HIV to her infant (Peltier, Ndayisaba, Lepage, Griensven, Leroy et al., 2009:2415).

Coovadia et al., (2007:1107) conducted a study in Durban, South Africa and found that mixed feeding was associated with an increased HIV transmission rate, while exclusive breastfeeding had a lower transmission rate. This influenced the revision of the present UNICEF, WHO and UNAIDS infant feeding guidelines. Exclusive formula feeding has a 0%

HIV transmission rate but the rate of mortality from causes other than HIV is higher (Peltier et al., 2009:2415).

Despite HIV infection via breastfeeding in HIV exposed infants, breastmilk has been proved to be a cost effective intervention and is associated with good maternal and child health.

1.4 SIGNIFICANCE OF THE REVIEW

Individual study results can often not be generalised. By combining outcomes of various trials, this systemic review can yield reliable and evidence based results. The primary aim of this systematic review was to critically appraise and review the evidence based on the effectiveness of exclusive breastfeeding in the prevention of HIV transmission from mother to child as compared to exclusive formula feeding. Across the studies, the efficacy of exclusive breastfeeding has been determined through comparison with exclusive formula feeding and mixed feeding. The secondary aim was to summarise evidence on mortality and HIV free survival in HIV exposed breastfed infants. Therefore, results of this systematic review can inform practice and awareness can be raised regarding effective feeding options in HIV exposed infants in both, the community and amongst patients.

1.6 AIM

Before the commencement of the study, the following review question was posed: Is exclusive breastfeeding (with the use of antiretroviral therapy) effective in the prevention of mother-to-child transmission of HIV-1 infection as compared to exclusive formula feeding and/or mixed feeding. Therefore, the aim of the systematic review was to compare the effectiveness of exclusive breastfeeding versus that of formula feeding and/ or mixed feeding with the use of antiretroviral prophylaxis in the prevention of HIV-1 transmission from mother to child.

1.7 OBJECTIVES

Primary objective

1. To evaluate the evidence on exclusive breastfeeding in the prevention of mother-to-child transmission of HIV-1 infection as compared to exclusive formula feeding and/ or mixed feeding with the use of antiretroviral prophylaxis.

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Secondary objectives

1. To compare the mortality rates in exclusive breast-fed infants as compared to exclusively formula and/ or mixed-fed infants as measured up to 24 months.

2. To determine the HIV-free survival as measured up to 24 months in exclusive breast-fed infants as compared to exclusively formula and/ or mixed-fed infants.

1.8 HYPOTHESIS

It was hypothesised that exclusive breastfeeding with the use of antiretroviral prophylaxis is more effective than formula feeding (in instances where formula feeding is NOT acceptable, affordable, feasible, sustainable and safe) and/ or mixed feeding in the prevention of HIV-1 transmission from mother to child.

1.9 RESEARCH METHODOLOGY

1.9.1 Introduction

Rothstein, Sutton and Borenstein (2005:351), define a systematic review as a review of a clearly formulated question that involves systematically finding, critically appraising and combining evidence from scientific trials and aims at minimising bias and synthesizing evidence based results. According to Higgins and Green (2006:98-99), a small effect can be detected through systematic reviews; individual studies may not have significant outcomes, therefore, combining two or more homogenous studies through meta-analysis results in improved detection of treatment effects.

1.9.2 Criteria for considering studies for this review

1.9.2.1 Types of studies

Studies included in this systematic review were randomised controlled clinical trials (RCTs) and a cohort study. RCTs have an eligible and important study design which is important when dealing with questions on therapeutic effectiveness (Higgins & Green, 2006:60).

1.9.2.1a Types of participants

Studies on infants who were HIV-1 exposed (mother HIV positive during pregnancy) and were either exclusively breastfed or exclusively formula fed were considered in the review.

1.9.2.1b Types of interventions and comparisons

According to Glasziou (2001:121), an intervention will generally be a therapeutic procedure such as a treatment with a pharmaceutical agent or dietary requirements. In this review, experimental interventions from selected studies were to include exclusive breastfeeding (six months duration) compared to formula feeding and/ or mixed feeding under an antiretroviral prophylaxis.

According to Coutsoudis, Pillay, Kuhn, Spooner, Tsai and Coovadia (2001:472), outside the context of HIV, exclusive breastfeeding from 0-6 months is the single most effective strategy to reduce infant mortality worldwide. Furthermore, in cases of HIV exposed infants, there is 1% chance per month of HIV transmission through breastfeeding without antiretroviral prophylaxis: the longer the duration of breastfeeding, the higher the risk of HIV transmission (Leroy, 2007:9).

1.9.2.1c Type of outcome measures

It is vital for authors to state the outcome measures clearly and in a meaningful manner. They should be of importance to the policy makers as well as health care professionals so that they can give results based on care which is crucial to patient care (Higgins & Green 2006:60). In this systematic review, the outcome measures of interest are as follows:

Primary outcomes

1. HIV infection as measured up to 24 months

Secondary outcomes

1. Infant mortality measured up to 24 months

2. HIV-free survival as measured up to 24 months

1.9.3 Exclusion criteria

As stated in the protocol, studies showing an attrition rate of more than 15% were to be excluded. Due to longer duration of studies and a possibility of high attrition rate, a minimum of 20% loss to follow up was considered. Studies not reporting outcomes of interest were excluded.

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There are different reasons why study participants may be lost or withdraw from a study. This could be due to side effects of the study drug, loss of interest by participants, death, change of address or loss during follow-up (Higgins et al., 2006:203). Table 4.5 in chapter 4 shows some detailed reasons why most studies were excluded from the review.

1.10 SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

1.10.1 Electronic search strategy

Databases of health related documents (or similar) including PUBMED/MEDLINE (Medical Literature Analysis and Retrieval System Online), EMBASE, (Excerpta Medica Database), CINAHL (Cumulative Index of Nursing and Allied Health Literature), Cochrane Clinical Trial Register and Cochrane HIV/AIDS Group/CENTRAL (Cochrane Central Register of Controlled Trials) were searched extensively. A search of electronic journals was done. Breastfeeding and HIV textbooks, as well as HIV/AIDS conference proceedings were also accessed. There were no limitations to language or date during the search and the articles were peer reviewed publications. Both published and unpublished data were accessed. The medical search headings (MeSH terms) that were used for searching data included: exclusive breastfeeding, HIV, infant feeding, interventions, prevent HIV transmission, postnatal HIV transmission, randomised, randomized, randomisation and randomization. A general search strategy was adapted for each database.

1.10.2 Other sources

Links from electronic data or reference lists were referred to in order to source more studies. Glasziou (2001:1) states that this process is referred to as ‘snowballing’ and reviewers broaden their search using these methods; therefore, important studies are rarely missed. To obtain more data, study trialists, experts such as breastfeeding specialists, midwives, HIV counsellors, HIV conference proceedings and breastfeeding organisations were consulted.

1.11 DATA EXTRACTION AND ANALYSIS

1.11.1 Selection of studies

The strategy of critical appraisal and selection was adopted to identify the studies meeting the inclusion criteria. The primary reviewer, Angel Phuti (AP) assessed the titles of all the studies obtained during an extensive literature search. AP and OK (Oswell Khondowe)

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independently screened and eliminated the irrelevant ones. The abstracts of those remaining were also assessed to determine if they were eligible. Abstracts were read by both reviewers to assess for eligibility. Full articles of eligible studies were read and relevant information was extracted. Any discrepancies were resolved through discussions and Kim Harper (KH) was available for further consultations. A data extraction form was used to collect and extract information from the studies.

1.11.2 Assessment of methodological quality

To ensure data validity and reliability, the researchers (AP) and (OK), independently assessed the data quality using the Cochrane assessment tool. For any further consultations, a third reviewer (KH) was available.

Every included study was judged using six domains as follows: sequence generation, allocation concealment, blinding of participants, as well as personnel and outcome assessors, incomplete outcome data assessment outcome reporting and other sources of bias. Each question or domain was rated as either high risk, low risk or unclear. A judgement of each domain was then entered into Rev Man 5.1.0 and a risk of the bias table was obtained.

1.11.3 Data extraction and management

A standardised data extraction tool form was used to extract and collect the information relevant for this review. The reviewers independently extracted the data from the articles. Notes were then compared. Where there was a variance, the two reviewers discussed the variance and came to an agreement.

1.11.4 Measurement of treatment effect

The measure of effect that was to be used was the relative risk (RR) for dichotomous data with a 95% confidence interval (CI) and a p-value of 0.05 using the random effects model to accommodate potential bias. Relative risk is defined as the chance of developing a disease condition relative to exposure (Deeks, Higgins & Altman 2006:103). The meta-analysis method is available in the software Rev Man 5.1.0 for analyses (Deeks et al., 2006:101-136). A calculation of relative risk or RR and OR is as follows:

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Table 1.1: Calculation of relative risk or odds ratio

	Event	No event	Total
Intervention	A	B	a + b
Control	C	D	c + d

RR = risk of event in the intervention group [a/ (a+b)] ÷ risk of event in control group [c/ (c + d)] (Higgins et al., 2006: 102).

1.11.5 Dealing with missing data

Authors were to be contacted for missing data, as well as including articles which used the intention to treat analysis.

1.11.6 Assessment of heterogeneity

A statistical test strategy, the chi-squared test, I-squared test and forest plot, were used to measure or assess whether observed differences in results are compatible with chance alone (Higgins and Green, 2006:137-138). A more detailed summary on how the reviewers assessed heterogeneity is presented in Chapter 3.

1.11.7 Data synthesis (meta-analysis)

Rev Man 5.1.0 was used for meta-analysis. The measure of effect of choice was the relative risk (RR) with a 95% confidence interval (CI) for dichotomous data and a p-value of 0.05. The random effects model was incorporated to accommodate heterogeneity that could not be explained thus eliminating potential bias. To demonstrate and illustrate the effects of interventions, forest plots were used.

1.11.8 Subgroup analysis and sensitivity analysis

Due to clinical diversity across the studies, subgroup analysis was done. Measurements of the outcomes; HIV infection, HIV free survival and infant mortality were done at different

ages and there could be unknown inconsistencies. Sensitivity analysis was incorporated during meta-analysis to determine if the same results could be obtained.

1.12 ETHICAL CONSIDERATIONS

Permission to conduct this study was sought from the Ethics Committee at Stellenbosch University. A panel of research methodology experts in the Division of Nursing reviewed the protocol and permission for the study to proceed was given by the Ethics Committee. The registration number assigned to the protocol was N10/11/391. All trials used in the review were registered by their relevant Ethics Committee.

1.13 DISSEMINATION OF RESULTS

A report in thesis form was submitted as part of the fulfilment of a Master's of Nursing (MCur) degree to Stellenbosch University. The researcher will present the results at a relevant conference and will publish in an accredited journal. Reader friendly copies will be distributed to a variety of educational places and health institutions. These will include universities, community health centres, policy makers and community libraries or newspapers.

1.14 STUDY LAYOUT

Chapter 1: Introduction: Scientific foundation of the study

The chapter focuses on the overview of the research field, background, rationale and preface of research methods.

Chapter 2: Literature review

This chapter contains information on what is currently known or documented about the research topic.

Chapter 3: Research methodology

It elaborates in detail on the methodology used to conduct the systematic review, as well as the study design.

Chapter 4: Results, Data synthesis, Results interpretation and presentation

The chapter shows how the data is managed and presented in tables and graphs. The reviewer discusses the results in relevance to the hypothesis and research question.

Chapter 5: Conclusion/recommendations

A summary of the systematic review main findings is documented in this chapter and the reviewer gives evidence based recommendations.

1.15 OPERATIONAL DEFINITIONS

- **A systematic review:** It is a review of a clearly formulated question that involves systematically finding, critically appraising and combining evidence from scientific trials and aims at minimising bias and synthesizing evidence based results (Rothstein, et al., 2005: 351).
- **AIDS:** An abbreviation for Acquired Immunodeficiency Syndrome.
- **Antiretroviral therapy:** It is the therapy given to reduce HIV transmission from mother to infant or to treat the infection. In developing countries a single dose of nevirapine remains widely used and has been proven to reduce HIV transmission via breast milk during the early postpartum period when the majority of breast milk transmission occurs (Lehman et al 2008:2).
- **Exclusive breastfeeding:** Implies that an infant receives only breast milk, and no other liquids or solids, not even water, with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines (Newell, 2004:1).
- **Formula feeding:** Infant milk artificially prepared with more or less similar contents as breast milk but does not contain colostrum. (Nolte 2007:249)
- **Meta-analysis:** A summary of past research using statistical techniques to transform findings of studies with related/identical hypothesis into a common metric and calculating the overall effect, the magnitude of effect and sub sample effect of interventions/relationships (Burns & Groove 2007:360). Meta-analysis statistically pools the results from previous studies into a single quantitative analysis that provides the highest level of evidence for an intervention efficacy (Conn & Rantz 2003:400).

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1.16 CONCLUSION

Chapter 1 consisted of the general foundation of the systematic review. It explicitly outlines how the reviewer conducted the research. It gives an overview on what to expect throughout the following chapters and will act as a guide and may give an understanding to the readers before proceeding to the fully detailed contents of the systematic review.

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CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

A literature review includes all written sources, usually published by scholars, relevant to the topic of interest. It involves finding, reading, understanding and forming conclusions about the published research and theory, as well as presenting it in an organised manner (Burns & Groove 2005:93). The main aim of this chapter is to conduct a critical analytical appraisal of the recent scholarly work on the topic. By determining what is already known about the topic, the researcher can obtain a comprehensive picture of the state of knowledge (Brink, Van Der Walt & Rensburg 2008:66) regarding the topic of interest.

2.2 DEFINITION OF EXCLUSIVE BREASTFEEDING

According to Newell (2004:1), exclusive breastfeeding is whereby an infant is fed with only breast milk, and no other liquids or solids, not even water, with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines.

2.2.1 Breastfeeding and HIV

For optimal growth, development and health, infants should be exclusively breastfed for their first six months. Such infants should then receive nutritionally adequate and safe complementary foods, while breastfeeding continues up to 24 months and beyond. This intervention is effective in cases of HIV-free breastfeeding mothers, otherwise the risk of mother to child transmission of HIV can double to about 40%, especially if antiretroviral prophylaxis and effective interventions are not followed (Newell, 2004:1).

HIV infected mothers may consider expressing and heat treating breastmilk as an interim feeding strategy:

- If antiretroviral drugs are temporarily not available; or
- To assist mothers to stop breastfeeding; or

- In special circumstances, such as low birth weight infants or otherwise ill infants in the neonatal period; or
- When the mother is unwell and temporarily unable to breastfeed or when temporary breastfeeding problems, such as mastitis, occur (WHO, 2009:20).

Laboratory evidence demonstrates that heat treatment of expressed milk from HIV infected mothers, if correctly done, inactivates HIV. Furthermore, there is no significant proof or evidence that heat treatment alters the nutritional content of the breast milk; hence, breast milk treated this way should be adequate to support normal growth and development WHO (2009:20).

2.2.2 Characteristics of breast milk

Breast milk consists of colostrum, transitional and mature milk (Nagin, 2008:1; Nolte, 2008:233; Leroy, 2007:6-7). Colostrum is the thick yellow milk secreted by the breasts during the first few days after delivery. Generally, it is a leftover mixture of materials present in the mammary gland and ducts at delivery (Leroy, 2007:6; Nagin 2008:1). According to Leroy (2007:6), it gradually evolves into mature milk at 3-14 days postpartum. Colostrum has a low protein and fat content (Nolte, 2007:233), and contains more antibodies and white blood cells than mature breastmilk (Leroy 2007:6). It aids in the formation of protective bacteria, or bifidus flora, in the gastrointestinal tract and also eases the movement of meconium (Nagin 2008:1). According to Horvath et al., (2010:4), epidermal growth factor in colostrum helps to make the gastrointestinal tract less permeable to viral infection. Nagin (2008:1), states that breast milk consists of water as its largest component (90%), oligosaccharides, vitamins, minerals, hormones, growth factors and protective agents. It also has 10% solids for energy and growth (Nagin 2008:1).

During the past decades, breastfeeding has been reinforced to improve both maternal and child health. Holmes and Salvage (2007:1065), indicated immediate and long term benefits of breastfeeding which includes it being a cost effective intervention for child survival and could prevent 13-15% of child deaths in low income countries. Breastfeeding protects against common infections such as diarrhoea, pneumonia, neonatal sepsis and otitis media. According to Newell (2004:5), a study conducted in Brazil found that infants who were not breast-fed were 17 times at higher risk of hospital admission (OR 16.7, 95% CI, 7.7-36.0).

A systematic review by Hovarth et al., (2010) concluded that in HIV cases, complete avoidance of breastfeeding (exclusive formula feeding) is efficacious in preventing MTCT of

HIV but also associated with high morbidity. The systematic review indicated that extended antiretroviral therapy reduces the chances of MTCT of HIV infection. Horvath et al., systematic review is different from this review; their inclusion criteria consisted of trials whose participants had extended antiretroviral therapy and standard regime while this review's trial participants were on standard regimes only which is currently on the national policy. Some of the studies included in Horvath's meta-analysis didn't compare exclusive breastfeeding with exclusive formula feeding. Therefore the reviewer aimed at focusing on the current health problem of exclusive breastfeeding versus exclusive formula feeding under a standard antiretroviral regime.

2.3 DEFINITION OF EXCLUSIVE FORMULA FEEDING

The process of feeding a child who is not receiving any breast milk with a diet that provides all the necessary nutrients that the child needs is termed 'replacement feeding' (Leroy 2007:8; Newell 2004:6).

Formula feeding involves the use of commercial infant formula that is formulated industrially in accordance with applicable Codex Alimentarius standards to satisfy the nutritional requirements of infants during the first six months of life up to the introduction of complementary foods (Newell 2004:1). According to Nolte (2007:249), although the manufacturers of infant formulas attempt to produce a product similar to breast milk in quantity, some elements are only present in breastmilk, e.g. antibodies.

Examples of commonly used modified milk formulas or breastfeeding substitutes are:

- Whey protein-dominant starter formulas (Nan, S26, and Similac 60/40): Infants under four months of age should preferably have a whey-(lactalbumin) predominant formula. According to Vivatvakin, Mahayosnond, Theamboonlers, Steenhout and Conus (2010:473), formulas predominately containing whey as a source of protein are considered to be similar to breast milk in terms of composition. Whey has been shown to have some benefits, such as stimulating the growth of bifidobacteria. Furthermore, in infants, gastric emptying is more rapid after whey ingestion than after casein ingestion (Vivatvakin et al., 2010:473).

- Casein-predominant starter formulas (Lactogen No. 1, SMA, and Similac): These formulas can be given to the larger full term newborn (birth weight ≥ 3300g) at full strength, as they are complete and nutritionally fully balanced.

- Biologically pre-acidified starter formula (Pelargon): This formula is only used in infants with mild digestive disturbances. It is suitable in cases where the risk of

contamination during preparation of bottle-feeds is high. It has some bacteriostatic properties, finer and more digestible curd. Fat, vitamin and iron content are similar to breast milk.

- High protein formulas (Lactogen No. 2, Infagro): to supplement protein intake in diet such as cereals or fruit, especially after introduction of solids.
- Full cream milk formulas (Klim, Nespray): appropriate for babies older than 8-12 months who should be on a full diet.

Adapted from Nolte (2007:250).

2.4 DEFINITION OF MIXED FEEDING

Mixed feeding is defined as the process of feeding a child breast milk and other fluids or food. This can disturb the lining or cause trauma to the gastrointestinal tract of the infant, hence the risk of mother to child transmission of HIV is higher (Fraser, Cooper & Nolte, 2006:366). According to the Department of Health of the Republic of South Africa (2008:115), mixed feeding carries the highest risk of HIV transmission and should be discouraged.

2.5 DEFINITION OF HIV

Human Immune (HI) Virus is a causative virus of AIDS (Acquired Immune Deficiency Syndrome). Mother to child (vertical) transmission of HIV can occur transplacentally in-utero, intra-partum, post-partum or through breastfeeding (Cronje & Grobbler, 2003:428). According to Leroy (2007:8), data suggest that the first six to eight weeks of breastfeeding could be a high risk period for the transmission of HIV.

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Table 2.1: Estimated absolute rates of mother-to-child transmission (MTCT) of HIV by timing of transmission, without interventions

	HIV transmission rate (%)		
Timing of HIV transmission	**No Breastfeeding**	**Breastfeeding through six months**	**Breastfeeding through 18 to 24 months**
During pregnancy	5-10	5-10	5-10
During labour	10-15	10-15	10-15
During breastfeeding	0	5-10	15-20
Overall	15-25	20-35	30-45

NB: Rates vary because of differences in maternal CD4 cell counts, RNA viral load and duration of breastfeeding.

Adapted from (De Cock, Fowler, Mercier, de Vincenzi, Saba, et al., 2000:1178).

Table 2.2: Rates of, and risk factors for overall mother-to-child transmission of HIV according to geographical location in antenatal clinics

	URBAN	**RURAL**
West and Central Africa	10-15%	Generally lower rates
East Africa	15-25%	5-10%
Southern Africa	Over 40%	25-38%
Caribbean, Central America, South America	0.1-5.0%	None reported
Asia (cities/provinces of Cambodia, India, Indonesia and Thailand)	1-5%	None reported
Eastern Europe	Over 1%, likely to increase	None reported

Adapted from (Leroy 2007:3).

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2.6 PATHOPHYSIOLOGY OF HIV

HIV is a retrovirus, which carries its genetic information in Ribonucleic Acid (RNA). On entry into the body, the virus infects cells which have the CD4 antigen (Le Mone & Burke 2000:293). Thereafter, the virus sheds its protein coat and uses an enzyme called reverse transcriptase to convert RNA to Deoxyribonucleic Acid (DNA). This viral DNA is then integrated into the host cell DNA and is duplicated in large numbers during normal cell division, infecting more lymphocytes (Le Mone & Burke, 2000:293; The Department of Health-South Africa, 2006b:202).

Within the cell, the virus may remain latent or become activated to produce new RNA and form virions. The virus then buds from the cell surface, disrupting its cell membrane and leading to destruction of the host cell. Although the virus may remain inactive in infected cells for years, antibodies are produced to its proteins, a process known as seroconversion. These antibodies are usually detectable 6 weeks to 6 months after initial infection. The antibodies seem to have little effect on the virus (Le Mone & Burke 2000:293).

CD4 cells (also known as T4 or helper T cells) are lymphocytes (a type of white blood cell), which are key in both humoral and cell mediated immune responses. These are the main target cells for HIV. Their numbers decrease during HIV infection, and their level is used as a marker of progression of the infection (Newell 2004:6; Leroy 2007:4).

2.6.1 Mechanisms of transmission of HIV through breastfeeding

Despite evidence showing that HIV is present in breastmilk (Nduati, John, Mbori-Ngacha, Richardson, et al., 1995:1461), mechanisms of transmission through breastfeeding remain incompletely understood.

According to Newell (2004:11), after ingestion of HIV-1 infected breastmilk, infant gut mucosal surfaces are the most likely site of transmission. Cell-free or cellular HIV-1 may penetrate to the submucosa in the presence of mucosal breaches or lesions, or via transcytosis through M-cells or enterocytes expressing specific receptors.

2.6.2 Characteristics of the mother and infant in relation to HIV

A number of maternal and infant characteristics have been associated with an increased risk of HIV transmission(Horvath et al., 2010:4). Clinical, immunological and virological factors in mothers, as well as infant feeding patterns, affect postnatal transmission (Leroy 2007:11).

Maternal

Recent HIV infection: (The acute viral syndrome of "primary" HIV infection.) At this stage, there is usually high plasma viremia and frequently a marked decrease in CD4+ cells (Hoffman, Rockstroh & Kamps, 2007:26). A low CD4+ cell count is a risk factor for late postnatal transmission of HIV (Horvath et al., 2010:4). According to Leroy (2007:12), high levels of the virus in the blood, and probably also in breastmilk are seen in primary HIV infection, when the rate of postnatal transmission has been estimated to be nearly 30%. A study conducted by the ZVITAMBO study group and Humphrey (2005:704), found that women with CD4 cell counts less than 200 cells/µl were five times more likely to transmit HIV during breastfeeding compared with women with CD4 cell counts over 500 cells/µl.

Mode of delivery: According to (Leroy 2007:4) and Fraser et al., (2008:366), vaginal delivery and duration of delivery, which increase the contact between infant and infected cervico-vaginal secretions and blood, are linked to MTCT when compared to elective caesarean sections.

Breast conditions: Recent studies confirmed the association of transmission of HIV through breastfeeding with maternal breast abnormalities such as breast abscess, mastitis, and nipple lesions (Horvath et al., 2010:4). Clinical and subclinical mastitis has been associated with a transmission risk (Newell 2004:14; Leroy 2007:13; Horvath 2010:4). According to Horvath (2010:4), ingestion of inflammatory cells related to the bacterial infection of the breast contributes to breastfeeding transmission of HIV.

Nutritional: According to Fraser et al., (2008:366), if a woman is more malnourished, the maternal disease will progress more rapidly and thus the risk for mother-to-child transmission will also increase. A multivitamin supplement may improve the wellbeing and increase the chances of resistance to infection. HIV/AIDS causes people to have high needs of certain vitamins and minerals due to their body demands to build and repair tissues. Therefore, a vitamin supplement with added minerals is essential (WHO 2003:10).

Infant

Gestational period of birth: Preterm birth places the infant at a higher risk of mother-to-child transmission compared to full-term births. This is due to the physiological differences between the two which includes poor development of the immune systems and well as the physical body parts. This exposes them to the HI virus. (Fraser et al., 2008:366).

Duration and pattern of breastfeeding: Exclusive breastfeeding has been associated with a lower risk of postnatal transmission of HIV as compared to non-exclusive breastfeeding, that is, breastfeeding with formula, other fluids (water, fruit juice) or solids (baby food) (Leroy 2001:15; Iliff, Tavengwa, Zunguza, Marinda, Nathoo et al., 2005:699). The introduction before the age of 3 months of solid foods or animal milk to breastfeeding infants born to HIV positive mothers was associated with a fourfold greater risk of postnatal transmission at 6 months compared with exclusive breastfeeding (Iliff et al., 2005:703).

Oral thrush: According to Newell (2004:14), oral thrush damages the mucous membranes; therefore, it is associated with an increased risk of transmission through breastfeeding. It is difficult, however, to determine which of the two is the cause or the effect, since thrush may be a feature of early HIV-1 infection (Epinkin, Witkor, Satten, Adjorlolo-Johnson, Sibailly, Ou et al., 1997:1055).

2.6.3 Detection of HIV; diagnostic tests

There are different diagnostic tests used to detect the HIV virus. According to Gürtler (1996:176), the diagnosis is normally made indirectly, that is through the demonstration of virus specific antibodies (anti-HIV) by ELISA or agglutination. Reactive results are confirmed by western blot (immunoblot) or further specific tests such as competitive ELISA (Gürtler 1996:176). Direct diagnosis of HIV infection is also possible through the demonstration of the infectious virus (using cell culture - this is only possible in laboratories of at least biological safety level 3), viral antigen (p24 antigen ELISA) or viral nucleic acid (that is viral genome; NAT= nucleic acid testing) (Wolfgang & Korsman 2007:41).

HIV antibody diagnosis-two screening assays; a screening test and at least one confirmatory test are required for the testing of HIV antibodies. To exclude inadvertent mix-ups of samples, a second blood sample from the same patient should generally be tested. Only then should the diagnosis of HIV infection be communicated to the patient in cases of unexpected seropositivity (Wolfgang et al., 2007:41).

Most screening tests are based on the ELISA principle (enzyme linked immuno sorbent assay). Screening tests must be extremely sensitive to minimise the chance of yielding a false-negative result (Wolfgang et al., 2007:42).

Enzyme linked immunosorbent assay (ELISA) screening test: This is the most widely used screening test for HIV infection. It is a test for HIV antibodies and does not detect the virus, therefore, a client may have a negative ELISA test result early in the course of infection before detectable antibodies have developed (Le Mone et al., 2000:299). This phenomenon is called the “diagnostic window” or “window period" (Busch & Satten 1997:117). Furthermore, false positives do occur; hence it is always necessary to do a confirmatory test which should be communicated to the patient intensively (Wolfgang et al., 2007:44).

Confirmatory assay: For confirmation of a positive or reactive test, a western blot antibody test or an immunofluorescence assay (IFT or IFA) is done (Wolfgang et al., 2007:44). According to Le Mone et al. (2000:299), this test is more reliable but more time consuming and more expensive than ELISA. During this test, the patient's serum is mixed with HIV proteins to detect a reaction. If antibodies to HIV are present, a detectable antigen-antibody response will occur (Le Mone et al., 2000:300).

HIV nucleic acid testing (NAT): It usually entails a Polymerase Chain Reaction (PCR). If done at birth, or from two weeks of age it will detect babies infected in utero or perinatally, therefore the recommended age for reliable HIV PCR testing in babies is ≥ 4 weeks (Wilson, Naidoo, Bekker, Cotton & Maartens, 2005:44). According to Wolfgang et al., (2000:45), this detection of a viral nucleic acid (viral genome) is laboratory tested from EDTA (ethylene diamine tetra acid) whole blood or EDTA plasma.

Rapid tests: Also known as the "bedside", "point of care" or "simple/rapid" test. This test is used when results are needed urgently, for example in emergencies. They are based on one of four immunodiagnostic principles: particle agglutination, immunodot (dipstick), immunofiltration or immunochromatography. The results are normally available within fifteen to thirty minutes. A capillary blood sample is obtained through venipunture (from a finger tip). A reagent is added on the drop of blood and a "built in" internal control detects if the reagent is sufficient; if this control shows up, the results should not be accepted. One band indicates a negative result while two indicate a positive result (excluding the control band) (Wolfgang et al., 2000:45).

CD4 (Cluster of differentiation) cell count: This is used to monitor the disease progress and guide treatment therapy (Le Mone et al., 2000:300; Newell 2004:4; Leroy 2007:6).

2.7 INTRODUCTION- AIDS (Acquired Immune Deficiency Syndrome)

AIDS is disease of the human immune system caused by HIV and results in development of infections including opportunistic infections such as karposi sarcoma, candida albicans, cytomegalovirus, pneumocystis carinni and tumours that do not affect people with working immune systems (WHO 2009:4).

2.7.1 WHO clinical staging of HIV/AIDS

The clinical staging and case definition of HIV for resource-constrained regions is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4 cell count. This staging system is used in many countries to determine eligibility for antiretroviral therapy, particularly in settings in which CD4 testing is not available. Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS. These stages are defined by specific clinical conditions or symptoms (WHO 2009:5-6).

2.8 MANAGEMENT STRATEGIES OF HIV/AIDS

2.8.1 Non-drug management of HIV

According to the Department of Health in the Republic of South Africa (2006a:203), counselling is an extremely vital part of the successful care of children with HIV infection and their families. Specific matters requiring attention are:

- The implications of the disease for the family
- Implications of the treatment and understanding of the condition and its care.

On completion of counselling, the family should be able to make informed decisions taking all this information into account.

According to Fraser et al., (2008:667), a newly diagnosed pregnant woman must be offered intensive post-test counselling on the following aspects: effects of pregnancy on HIV infection, risk of transmission of HIV to foetus and newborn, option of termination of pregnancy, option for treatment in pregnancy and infant feeding. Other aspects include advantages and disadvantages of breastfeeding, disclosure of results to the male partner

and family, the need for follow-up of both woman and child and future fertility management (Fraser et al., 2008:367).

2.8.2 Drug management of HIV

Currently, infants are given doses of antiretroviral prophylaxis. Antiretroviral therapies decrease the viral load. Such prophylaxis is designed to protect the uninfected infant while exposed to infection through breastfeeding. The regimes are taken during pregnancy, intrapartum and postnatally by mothers, as well as infants' post-partum.

In 2009, the South African National AIDS Council (SANAC) Treatment Technical Task Team (TTT), finalised recommendations for changes to the national standard treatment guidelines for adult and paediatric management and treatment, as well as changes in the prevention of the mother-to-child-transmission of HIV (PMTCT) guidelines, moving away from monotherapy to dual therapy. As announced on World Aids day 2009 by President Zuma, the changes to the guidelines were not to meet the Presidential mandates only, but to bring them in line with international recommendations and ensure the use of more efficacious drugs, including the phasing out of stavudine from the national antiretroviral (ART) programme (Serenata & Bekker, 2010:28).

Pregnant women with a CD4 count less than 350 cells/µl meet the eligibility criteria to start antiretroviral therapy within two weeks of receiving their CD4 result and choosing to start lifelong antiretroviral therapy (ART). If the CD4 count is more than 350 cells/µl, these pregnant women follow the national PMTCT guidelines, namely:

- Zidovudine from 14 weeks - oral, 300mg 12 hourly
- Single-dose nevirapine (NVP) - oral, 200mg at onset of labour and zidovudine - oral, 300mg 3 hourly during labour to delivery
- Tenofovir and emtricitabine single dose after delivery.

If a woman presents in labour without having started either ART or the PMTCT regimen at 14 weeks, she should still receive the single-dose nevirapine and zidovudine 3-hourly and tenofovir and emtricitabine as per above (Serenata & Bekker 2010:28-30).

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Table 2.3 National regimens for infants in South Africa (Department of Health 2010:11)

Infants	Regimen	Comments
Mother on life long ART	NVP- 0.2ml/kg at birth and then daily for 6 weeks irrespective of infant feeding choice	
Mother on PMTCT	NVP-0.2ml/kg at birth and the daily for 6 weeks continued for as long as any breastfeeding.	If baby is formula fed, baby can stop NVP at 6 weeks
Mother did not get any ARV before or during delivery	NVP-0.2ml/kg as soon as possible and daily for at least 6 weeks continued for as long as any breastfeeding	Assess ART eligibility for the mother within two weeks
Unknown maternal status because orphaned or abandoned	Give NVP-0.2ml/kg immediately. Test infant with rapid HIV test. If positive, continue NVP for six weeks. If negative, discontinue NVP	Follow-up 6-week HIV DNA PCR

2.9 EXPERIENCES ON INFANT FEEDING CHOICES ACROSS THE WORLD

Women around the world are faced with a lot of issues surrounding breastfeeding and HIV. In Botswana, these HIV positive women are advised not to breastfeed by the health care workers. Shapiro, Hughes, Ogu, Kitch, Lockman, et al., (2009:1) (Mmabana study), conducted a clinical trial with a goal of comparing the suppression of the viral load at delivery and throughout breastfeeding among women allocated to receive different ARV regimens (HAART at 28 weeks). The goal was to determine the mother-to-child transmission rate after six months of breastfeeding among all women who received ARV therapy. The study produced the lowest rate (1%) of mother-to-child transmission in comparison with other studies done in Africa. Despite this, health care workers are not convinced by these results and are not confident to prescribe it (Balopi 2010:1).

In Kwazulu-Natal, women who are HIV positive, face different challenges on infant feeding choices. They are not well informed on the best feeding choice that is relevant to their socio-economic status (Seidel, Sewpaul & Dano 2000:26-27). Health care workers tend to prescribe formula milk to mothers whose last baby was known to be HIV positive, which is normally a special low lactose diet which is expensive, not a commercial one (Seidel et al., 2000:30). According to Agu, Peltzer, Seager, Setswe, Wabiri and Banyini (2009:14), infant feeding options should be discussed with mothers, and for each woman, the acceptability, feasibility, affordability, sustainability and safety (AFASS) of exclusive formula feeding should be discussed. If the AFASS criteria are not met, recommendation for exclusive breastfeeding is, therefore, essential (Agu et al., 2010:14). Some women disclosed to being abused by male family members if they chose not to breastfeed and also experienced negative attitudes by nurses if they chose exclusive formula feeding. These experiences result in mixed feeding (Seidel et al., 2000:30).

A qualitative study in Nigeria conducted by Sadoh (2009:31-32), found that about 21% of mothers could not adhere to exclusive breastfeeding after opting for it. These mothers failed to exclusively breast feed their infants and ended up mixed feeding. Twenty-three percent (23%) of these mothers had to recommence breastfeeding at 4 to 6 months of their infant's life. The reasons given were pressure, especially from extended family, and a case where the infant was said to have refused formula. Some had not disclosed their serostatus to their partners. About 77% mothers gave their babies "token" breast milk to pacify the child, especially in public (culturally, doing this to a crying baby is an expected behaviour). Some mothers would do this when they were around friends as proof that they did not have anything against breastfeeding (Sadoh et al., 2009:31-32). Mixed feeding results accounts for more infections than other modes of infant feeding. In a study in Durban, infants who received both breast milk and other feeds were significantly more likely to be infected by 15 months of age (36%), than those who were exclusively breast-fed (25%) or formula-fed (19%) (Coutsoudis 2001:380).

2.10 CONCLUSION

There are various interventions to prevent MTCT of HIV. Post exposure prophylaxis using antiretroviral drugs after exposure to bodily fluids from HIV-seropositive patients is done as recommended per institution (Gibbon 2005:307). Avoidance of unprotected sexual intercourse during pregnancy and breastfeeding mostly prevents infection (Fraser et al., 2008:366**).**

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According to Gibbon (2005:307), adherence to prevention of mother-to-child Transmission of HIV (PMTCT) programmes by pregnant mothers is vital. Extended antiretroviral prophylaxes to the infant (nevirapine alone, or nevirapine with Zidovudine) are efficacious in preventing transmission (Horvath et al., 2010:2). The mode of delivery has an effect on the infection rate. Caesarean section delivery before labour and before ruptured membranes (elective caesarean section) can prevent MTCT of HIV (Horvath et al., 2010:3). Appropriate infant feeding choices are important; complete avoidance of breastfeeding is efficacious in preventing MTCT of HIV, but mixed feeding is associated with high transmission rates and replacement feeding is associated with high morbidity (Horvath et al., 2010:2; Coovadia et al., 2007:1107). According to Thior et al., (2006:795), exclusive breastfeeding with abrupt early weaning after 3-6 months, pasteurization, hot water bath, and microbicidal treatment of breast milk with alkyl sulphates have been proposed as methods to make breastfeeding safe.

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CHAPTER 3

RESEARCH METHODS

3.1 INTRODUCTION

Research methodology focuses on all the related processes of review execution. Validity and reliability of data collection tools is ensured hence the quality of the study (Higgins & Green 2006:79; Brink et al., 2008:11). This chapter elaborates this research methodology intensively in this study.

3.2 RESEARCH DESIGN

It is vital for a researcher to formulate a research question that is "understandable" and researchable so that research designs, data collection and analysis may be possible (Brink et al 2008:52). Systematic reviews have been found to be the highest ranked source of evidence-based research 'for efficacy of interventions' (Glasziou et al., 2001:53). According to Higgins and Green (2006:98-99), a small effect can be detected through systematic reviews. Individual studies may not have significant outcomes. However, combining two or more homogenous studies through meta-analyses results can improve detection of treatment effects.

Meta-analysis is now used in numerous scientific disciplines, summarising quantitative evidence from multiple studies (Rothstein et al., 2005:1). Systematic reviews are then advantageous to health care workers, policy makers, patients and clients since they manage fewer quantities of data that might vary. According to Higgins and Green (2006:15), when numerous, homogeneous, primary researched trials are all summarised into one form; it is easier to understand and manage the results. Higgins and Green (2006:16) state that meta-analyses of heterogeneous studies in systematic reviews are possible and a random effects model is used to accommodate heterogeneity.

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3.3 AIM

The researcher's aim of the systematic review is to compare the effectiveness of exclusive breastfeeding versus that of formula feeding and/ or mixed feeding with the use of antiretroviral prophylaxis in the prevention of HIV-1 transmission from mother to child.

3.4 OBJECTIVES

Brink et al., (2008:79) define objectives as 'clear, concise, declarative statements that are written in the present tense and usually focuses on one or two variables and indicate whether such variables can be identified, analysed or described. The objectives are as follows:

3.4.1 Primary objective

1. To evaluate the evidence on exclusive breastfeeding in the prevention of mother-to-child transmission of HIV-1 (HIV infection) as compared to exclusive formula feeding and/ or mixed feeding with the use of antiretroviral prophylaxis.

3.4.2 Secondary objectives

1. To compare the mortality rates in exclusive breast-fed versus formula and/or mixed-fed infants.

2. To determine the HIV-free survival at 24 months in exclusive breast-fed versus formula and/ or mixed-fed infants.

3.5 HYPOTHESIS

It was hypothesised that exclusive breastfeeding (with the use of antiretroviral prophylaxis) is more effective than formula feeding and/ or mixed feeding in the prevention of HIV-1 transmission of mother to child, morbidity and better chances of HIV free survival.

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3.6 SELECTION CRITERIA FOR STUDIES

3.6.1. Search strategy for identification of studies

Health databases including PUBMED/MEDLINE (Medical Literature Analysis and Retrieval System Online), EMBASE, (Excerpta Medica Database), CINAHL (Cumulative Index of Nursing and Allied Health), Cochrane Clinical Trial Register and Cochrane HIV/AIDS Group/CENTRAL (Cochrane Central Register of Controlled Trials) were searched extensively. A search of electronic journals which includes the Southern African Journal of HIV medicine (SAJHIV), HIV Medicine Journal, African Journal of AIDS Research (AJOR) and American Journal of Public Health was conducted. Textbooks on breastfeeding and HIV, as well as HIV/AIDS conference proceedings were also accessed. A follow up from reference lists was done to source more data. The medical search headings (MeSH terms) that were used for searching data included: exclusive breastfeeding and HIV, infant feeding, interventions, prevent, HIV transmission, postnatal HIV transmission, randomised, randomized, randomisation and randomization.

In addition, experts in the field of paediatrics, midwifery and HIV/AIDS were contacted for more relevant information and referral to other sources. There were no limitations to language or date during the search and the articles were peer reviewed publications, unpublished data and theses. The search period ranged between December 2010 and February 2011.

A general search strategy as shown below was adapted for each one of the databases:

1 Breastfeeding

2 “Breastfeeding (exclusively)”/

3 (Exclusive breastfeeding$ or breastfeeding exclusively$ or exclusive breast feeding$).tw.

4 Exclusive formula feeding/

5 Formula feeding exclusively

6 Mixed feeding$.tw.

7 or/1-6

8Infant feeding/

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9 Infant feeding challenges/

10 HIV/

11 Postnatal HIV transmission/

12 Mother to child transmission of HIV /

13 interventions /

14 HIV prevention /

15 ((interventions or prevention$) adj3 (infant feeding postnatal transmission or mother-to-child transmission via infant feeding)).tw.

16 HIV free survival/

17 HIV infection/

18 HIV free /

19 Clinical trials/

20 Trials.tw.

21 clinical studies/

22 (Clinical trials or clinical studies).tw.

23 (randomised or randomized or randomisation or randomization).tw.23 or 8-23

3.6.2 INCLUSION CRITERIA AND ELIGIBILITY FOR STUDIES

All the studies meeting the inclusion criteria studies had the PICO acronym (Participant, Intervention, Comparison, Outcomes). A well formulated question comprises of these four parts (Glasziou et al., 2001:14). This is demonstrated below:

3.6.2a Population/ Participants or patient group

It refers to infants that were HIV-1 exposed via breastfeeding and exclusive formula feeding.

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3.6.2b Intervention (treatment group: exclusive breastfeeding)

In this review, experimental interventions from selected studies included exclusive breastfeeding (six months duration under a certain antiretroviral prophylaxis).

3.6.2c Comparison

Formula feeding (under a certain antiretroviral prophylaxis) was compared to exclusive breastfeeding. None of the included studies compared exclusive breastfeeding to mixed feeding.

3.6.2d Outcomes (prevention of HIV transmission from mother to child)

Primary outcome

1. HIV infection as measured up to 24 months of life

Secondary outcomes

1. Infant mortality as measured up to 24 months

2. HIV-free survival as measured up to 24 months

Two reviewers: (AP, OK) independently assessed titles identified in the search strategy. If a title was considered to be relevant, its abstract was reviewed to determine whether the article might meet predisposed eligibility criteria (as above). An article that did not meet eligibility criteria was rejected. If the title or abstract left room for doubt that the article cannot definitely be rejected, the full text of the article was obtained. Full text articles which did not meet the inclusion criteria were excluded. If the article was not rejected, information from it may then be formally extracted using the data extraction form. Disagreements about the inclusion of studies were resolved by referring back to the original article and discussion until consensus was established between the two reviewers.

Studies included in the systematic review were those with eligible study designs, such as randomised controlled trials and cohort studies with good quality evidence. The research design used was a systematic review with meta-analysis. Quality assessed studies: Thior, (2006), Peltier, (2009) and Nduati, (2000) were statistically combined and analysed on Rev Man 5.1.0 into a single quantitative analysis. The aim was to provide the best level of evidence for efficacy of therapeutic interventions.

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3.7 EXCLUSION CRITERIA

As stated initially in the protocol, studies showing an attrition rate of more than 15% were to be excluded. Due to longer duration of studies and a possibility of a high attrition rate, a minimum of 20% loss to follow up was considered. Studies not reporting outcomes of interest were excluded.

3.8 DATA EXTRACTION AND MANAGEMENT

A data extraction form was used as a tool to determine which studies met the inclusion criteria. It consisted of all the predetermined inclusion criteria. Data retrieved included: study design (RCTS, cohort), study population (infants), interventions (exclusive breastfeeding), comparisons (exclusive formula and mixed feeding), outcomes (Infant HIV, Infant mortality and HIV free survival), setting, socio- economic status, date of study, sample size, number lost to follow up, risk of bias assessment, type of analysis and results .
The two reviewers independently extracted the data from the articles. Notes were then compared. Where there was a disagreement, the two reviewers discussed and reached consensus. A third reviewer was available for further clarification and input.

A data extraction form was piloted using two articles to determine if the actual study could be feasible using the same data extraction form. This enabled the researcher to determine if the systematic review will be feasible. A pilot study identifies the type of data necessary for meta-analyses. According to Lancaster, Dodd and Williamson (2004:307-312), a pilot study is a small experiment designed to test logistics and gather information prior to a large study. It improves the quality of the efficiency of the latter, and can reveal deficiencies in the design of a proposed experiment or procedure and these can then be addressed before the time and resources are then expanded into large scale studies.

3.9 ASSESSMENT OF METHODOLOGICAL QUALITY

To ensure methodological quality, two reviewers independently assessed the studies using the Cochrane 'risk of bias' assessment tool. The six areas that were considered in assessing risk of bias were: sequence generation; allocation concealment; blinding; incomplete outcome data assessment; selective outcome reporting and other risks of bias, using the ratings: low risk, high risk and unclear to each domain by the reviewers (AP) and (OK) independently. Any disagreements were resolved through discussions. These judgements were entered into a 'Risk of bias' table in Review Manager 5.1.0 (Review

Manager 2011) with a brief rationale for the judgements. Review Manager Version 5.1.0 then formulated the two tables: Risk of bias graph and Risk of bias summary (Cochrane Collaboration 2009). Table 3.1 below shows a Cochrane risk of bias assessment tool.

Table 3.1: Cochrane assessment tool for assessment of methodological quality
(Cochrane Collaboration 2009)

DOMAIN	REVIEW AUTHOR'S JUDGEMENT	LOW RISK	HIGH RISK	UNCLEAR
Sequence generation	Was the allocation sequence adequately generated?			
Allocation concealment	Was allocation adequately concealed?			
Blinding of participants, personnel and outcome assessors ***Assessment should be made for each main outcome (or class of outcome)***	Was knowledge of the allocation intervention adequately prevented during the study?			
Incomplete outcome ***Data assessments should be made for each main outcome (or class of outcome)***	Were incomplete outcome data adequately addressed?			
Selection outcome reporting	Are reports of the study free of suggestion of selective outcome reporting?			
Other sources of bias	Was the study apparently free of other problems that could put it at a high risk of bias?			

Table 3.1 shows the Cochrane methodological quality/risk of bias assessment tool that was used for data validation. Each question or domain was rated as either high risk, low risk or

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unclear. The following paragraph explains in detail for each criteria how it was judged as high risk, low risk or unclear.

Random sequence generation

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it would produce comparable groups. We assessed the method as:

• low risk of bias (any truly random process, e.g. random number table; computer random number generator);

• high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or

• unclear risk of bias.

Allocation concealment

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as:

• low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

• high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);

• unclear risk of bias.

Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. Assessing blinding separately for different outcomes or classes of outcomes was done.

Methods were assessed as:

• low, high or unclear risk of bias for participants;

• low, high or unclear risk of bias for personnel.

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Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as: low, high or unclear risk of bias.

Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included study, and for each outcome or class of outcomes, a description of the completeness of data including attrition and exclusions from the analysis were made. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion were reported. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data that was included in the analysis that the reviewer made.

Methods were assessed as:

• low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups and is unlikely to influence the outcome; missing data have been imputed using appropriate methods);

• high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);

• unclear risk of bias.

Selective reporting (checking for reporting bias)

The chances of selective outcome reporting bias will be investigated. An assessment of the methods as either low risk, high risk and unclear risk of bias as clarified below was performed.

• Low risk of bias (where it is clear that all prespecified outcomes of the study and all expected outcomes of interest to the review have been reported);

• high risk of bias (where not all the pre-specified outcomes of the study have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

• Unclear risk of bias.

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Other bias (checking for bias due to problems

We described for each included study any important concerns we had about other possible sources of bias in each included study.

The reviewers independently assessed whether each study was free of other problems that could put it at risk of bias:

• low risk of other bias;

• high risk of other bias;

• unclear whether there is risk of other bias.

Overall risk of bias

Explicit judgments about whether studies are at high risk of bias were done, according to the criteria given in the *Handbook* (Higgins 2011:203). With reference to the above, we assessed the likely magnitude and direction of the bias and whether we consider it, is it likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses.

3.10 MEASUREMENT OF TREATMENT EFFECTS

The effect measure of choice was the relative risk (RR) with a 95% confidence interval (CI) for dichotomous data using and a p-value of 0.05. A random effects model was used to accommodate potential bias and heterogeneity. Studies were heterogeneous, the outcomes were measured at different months across the included studies and there could be inconsistencies. In homogeneous studies, a fixed effect model is used. To demonstrate and illustrate the effects of interventions, forest plots were used.

3.11 UNIT OF ANALYSIS ISSUES

The included studies, Thior (2006) and Nduati (2000), randomly assigned participants to either exclusive breastfeeding or formula feeding. Peltier (2009) conducted an interventional cohort study and the participants chose the feeding option for themselves. No random allocation of the intervention was used.

3.12 DEALING WITH MISSING DATA

There were attrition levels in the included studies. Sensitivity analysis was incorporated during meta-analysis to explore if there could be a variance between the results which

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should be taken into consideration. The included studies have all been analysed on an intention to treat basis when the trials were conducted. All the participants were analysed according to the group they were allocated to regardless of whether or not they received the allocated treatment or completed the study. The attrition number in each was calculated as the number randomised in the study minus the number whose outcomes of interest are missing.

3.13 DATA ANALYSES AND SYNTHESIS

Data was quantitatively analysed. A statistical tool, Review Manager Version 5 (RevMan 5.1.0) designed by the Cochrane Collaboration was used was used for meta-analyses. Meta-analyses were performed through statistical combination of outcomes from the three heterogeneous studies using the random effects model and standard mean difference. Included studies were intensively screened for methodological quality and combined to statistically analyse the data, hence increasing chances of detecting an effect. An advantage of applying meta-analysis is increasing power in small studies and this can detect small effects (Deeks et al., 2006:98). When two or more are combined, there is a high chance of detecting an effect (Deeks et al., 2006:97). In addition, it helps in answering questions that are not reflected by individual studies and resolving arguments arising from conflicting studies. This statistical analysis of findings allows the degree of conflict to be formally assessed for different results to be explored and quantified.

The effective measure of choice was a risk ratio with 95% confidence intervals for dichotomous data using a random effect meta-analysis. In cases where there are no heterogeneity suspected, a fixed effect method using weighed mean difference (WMD) for continuous or dichotomous data would be the model of choice. (Deeks et al., 2006:97-132). Forest plots were then used to demonstrate the effect of interventions.

3.14 ASSESSMENT OF HETEROGENEITY

According to Deeks et al., (2006:136) heterogeneity occurs when the included studies show diversity of participants, methodology, outcomes or statistics. If confidence intervals for the results of individual studies have a poor overlap, this generally indicates the presence of statistical heterogeneity (Deeks et al., 2006:137). Inconsistency gives incorrect and unreliable results in the end, especially if meta-analysis is mistakenly done.

To overcome this, the effective measure of choice was a risk ratio with 95% confidence intervals for dichotomous data using the random effects model. A statistical test strategy; the I-squared test (I^2) was used to measure heterogeneity using the formula $I^2 = (Q–df / Q) X 100\%$. Q implies chi-squared statistics while df is the degrees of freedom. This describes the percentage of the variability in effective estimate that is due to heterogeneity rather than chance. Proportion of variation, in effect, estimates between the included studies which were due to heterogeneity. An I-squared test of 0-40%, 41-60%, 61-75% and 76-100% were considered as not important, moderate, substantial and considerable heterogeneity respectively.

The p-value (P stands for probability) was used to determine the significance of heterogeneity. (Deeks et al., 2006:137). A p-value of 0.1 was used as an indicator of heterogeneity. (Deeks et al., 2006:137). Heterogeneity was also explored through subgroup analyses. Forest plots were then used to demonstrate the effect of interventions.

3.15 SUBGROUP ANALYSIS AND INVESTIGATION OF HETEROGENEITY

Heterogeneity was explored through subgroup analysis. Due to the wide variance in variables across studies, it was important to 'split' the studies so as to investigate heterogeneous results (Deeks et al., 2006:141). During subgroup analysis, the studies were grouped according to the consecutive ages that the outcomes were measured (6, 7, 9) or of the infants developmental stages (6, 9, 18 and 24 months). Subgroups were limited so as not to produce misleading results.

3.16 SENSITIVITY ANALYSIS

Sensitivity analysis was incorporated during meta-analysis to determine if the same results could be obtained. This was due to the fact that the outcomes of different trials included in the study were measured at different months therefore; there could be unknown inconsistencies between results across studies. Thior (2006) measured their outcomes at 7, and 18, Peltier (2009) at 9 months and Nduati (2000) at 6, 18 and 24 months. Deeks et al., (2006:151), elaborates that a re-analysing of the data is performed using a range of results for studies where there may be uncertainty about the results and this cannot be resolved by contacting the authors.

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3.17 VALIDITY AND RELIABILITY

Reliability is the consistency and dependability of a research instrument to measure a variable and yield the same results if used repeatedly over time on the same person or if used by two researchers (Brink et al., 2006:164-165).

Validity can either be internal or external. External validity is the degree to which study results can be generalised to other people and other research settings. Internal validity refers to the degree to which changes in the dependent variable (effect) can be attributed to the independent or experimental variable (cause). Instrument validity seeks to ascertain whether an instrument accurately measures what it is supposed to measure, given the context in which it is applied (Brink et al., 2006:159-165).

Data quality of included studies was assessed in the analysis. Studies were validated through assessing whether their designs and conduct are likely to prevent systematic errors or biases. To ensure this, a standardised Cochrane assessment tool was used. The three reviewers (AP), (OK) and (KH) are knowledgeable in systematic reviews and have attended research methods courses. In addition Prof. Hofmeyr, an expert in obstetrics, HIV/AIDS trials and systematic reviews was repeatedly consulted.

According to Higgins and Green (2006:81-82), the Cochrane assessment tool 'investigates' the sources of systematic bias in studies screened which are selection bias, performance bias, attrition bias and detection bias. The chi-squared and I-squared test were used for the assessment of heterogeneity.

3.18 ETHICAL CONSIDERATIONS

Permission to conduct this study was sought from the Ethics Committee at Stellenbosch University. A panel of research methodology experts in the Division of Nursing reviewed the protocol and permission for the study to proceed was given by the Ethics Committee. The registration number assigned to the protocol is N10/11/391. All trials used in the review were registered by their relevant Ethics Committee.

3.19 DISSEMINATION OF RESULTS

A report in thesis form will be submitted as part of the fulfilment of a Master's of Nursing (MCur) degree to Stellenbosch University. The researcher will present the results at a relevant conference and will publish it in an accredited peer reviewed journal. Reader

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friendly copies will be distributed to a variety of educational places and health institutions. These will include universities, community health centres, policy makers and community libraries or newspapers.

3.20 LIMITATIONS

The systematic review was based on relatively few articles and methodological weakness could influence conclusions of the study. There was also considerable variability across studies included in terms of timing used in measuring the outcomes possibly limited comparisons of results.

3.21 CONCLUSION

Chapter 3 gave a detailed elaboration of the research design and gives the reader a clear overview on how the research was conducted.

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CHAPTER 4

RESULTS

4.1 INTRODUCTION

This chapter presents the results of the systematic review. The synthesized data is managed and presented in tables and graphs. The reviewer discusses the results with relevance to the hypothesis and the research question.

Data analysis in quantitative studies such as systematic reviews basically entails that the analyst breaks down data into constituent parts to obtain answers to the research questions and to test the hypothesis. An analysis does not, in itself, answer the research question, therefore, the reviewer is required to interpret and give meaning to the results, thus answering the research question (De Vos, 2000:203).

4.2 OUTCOME OF SEARCH STRATEGY

4.2.1 Results of the search

Flow diagram 4.1 on the next page shows the results of the search strategy from PubMed, CINAHL, EMBASE and CENTRAL. The search brought about 243 citations. HIV/AIDS is a widely published subject and about 184 citations were sidelined because of irrelevancy. The 59 remaining citations generally indicated that the content was concerned about breastfeeding and other feeding options in relation to HIV/AIDS. An abstract of each citation was obtained of which 45 were excluded for not being actual studies; either news reports, comments or newsletters. Therefore, 14 full text articles were reviewed thoroughly. Eleven articles were excluded for various reasons such as high risk bias, irrelevant interventions and outcomes as shown in this chapter under ‘table of excluded studies’. Only 3 articles met the inclusion criteria Thior (2006), Nduati (2000) and Peltier, (2009).

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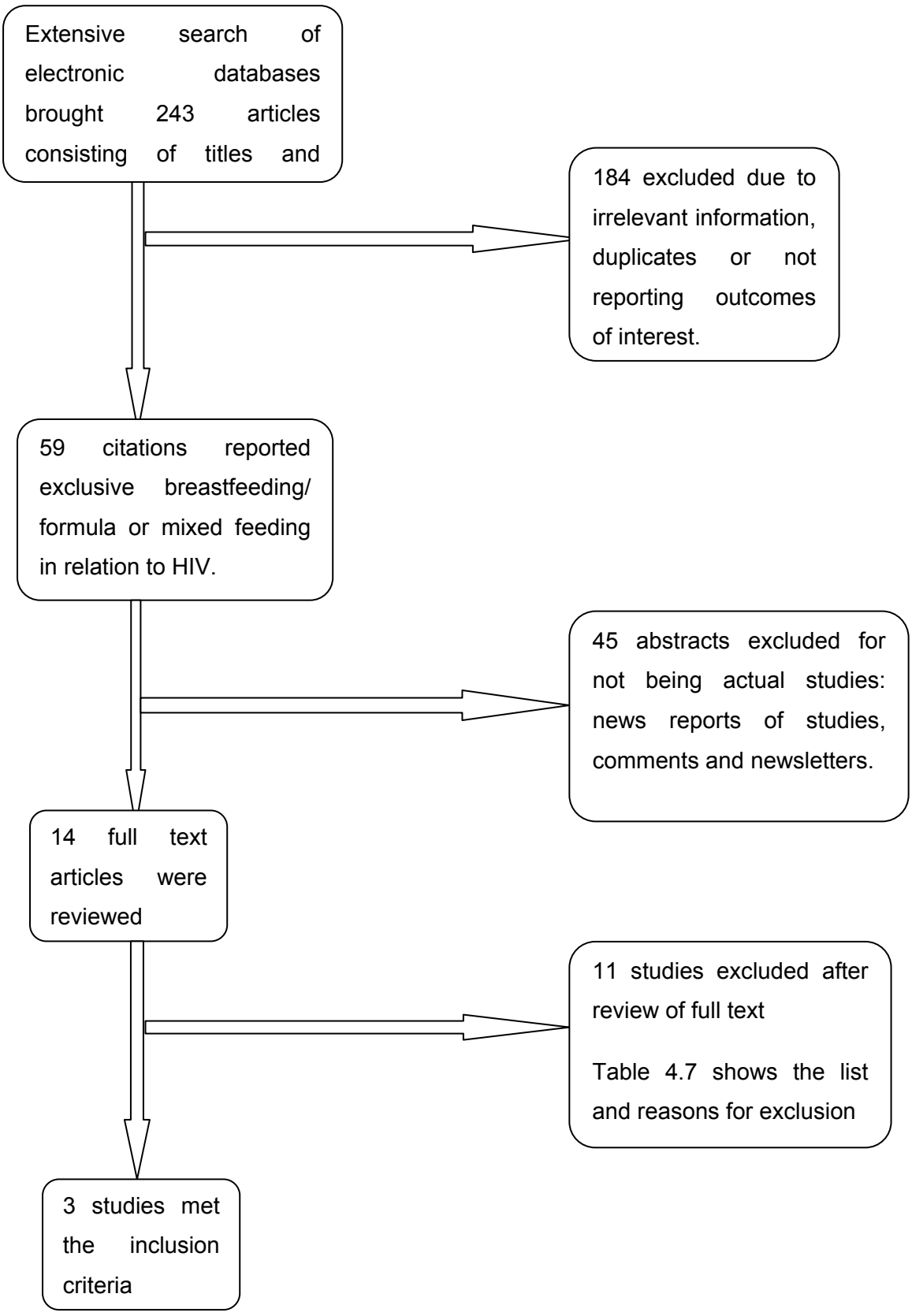

Figure 4.1: Flow diagram of results of various databases.

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4.2.2 Included studies

The tables below are a summary of the search results, included studies and their characteristics. The included studies were conducted in Botswana, Kenya and Rwanda. The sample size of all the participants included in the systematic review analyses was 2112. The included studies were all published in the English language and were published in peer reviewed accredited journals.

Table 4.1: Studies included in the review

Study ID	Citation
Thior, 2006	Thior, I., Lockman, S., Smeaton, L., Shapiro, R., Wester, C. ., Stevens, L., Moffat, C., Arimi, P., Ndase, P., Asmelash, A., Leidner, J., Novitsky, V., Makhema, J. & Essex, M. (2009). Breastfeeding plus infant zidovudine prophylaxis for six months vs. formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana. A randomised trial: The Mashi study. Journal of infectious diseases society of America, 199(3):414-418
Nduati, 2000	Nduati, R., John, G., Mbori-Ngacha., Richardson B., Overbaugh, J., Mwatha, A., Ndinya-Achola, J., Bwayo, J., Onyango, F. E., Hughes, J. & Kreiss, J (2000). Effect of breastfeeding and formula feeding on transmission of HIV-1: A Randomised Clinical trial. Journal of infectious diseases society of America, 283(9):1167-1174
Peltier, 2009	Peltier, C.A., Ndayisaba, G.F., Lepage, P., Van Griensven J., Leroy V., Pharm, C. O., Ndimubanzi, P. C., Courteille, O. & Arendt, V. (2009). Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. AIDS 2009, 23:2415-2423

Table 4.1 shows the three published studies, Thior (2006), Nduati (2000) and Peltier (2006), that were included in the analysis. They were published in accredited journals. The studies were screened for any methodological flaws that could give misleading results before inclusion as described in chapter 3. Chapter 4 clearly indicates how each study was

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assessed for inclusion, intensively screened for validity and reliability to eliminate high risk bias.

4.2.2.1 Characteristics of included studies

Table 4.2a: Characteristics of included study: Thior (2006)

Methods	2x2 Factorial Randomised clinical trial
Participants	1200 women who benefited from the HAART programme at different stages before delivery were randomised for two feeding options; 598 exclusive breastfeeding and 602 exclusive formula feeding before delivery. 1193 reached delivery of which 588 (7 stillbirths) were assigned to exclusive breastfeeding 591 (7 stillbirths) formula feeding. A total of 1079 live infants proceeded to the assigned feeding option
Interventions	The latter was designed as a superiority study to detect differences between exclusive breastfeeding plus infant zidovudine prophylaxis for 6 months and exclusive formula feeding plus infant zidovudine prophylaxis for 1 month. There was a total of 93.0% of full adherence to exclusive formula feeding as reported by mothers and a total of 17.5% by month 5 to exclusive breastfeeding while 75.5% reported mixed feeding and 7.5% reporting predominant breastfeeding
Comparisons	Exclusive breastfeeding plus infant zidovudine prophylaxis for 6 months vs. exclusive formula feeding and infant zidovudine prophylaxis for 1 month
Outcomes	Infant HIV infection, Infant mortality and HIV infection
Timeline	The outcomes were measured at 7 months and 18 months of age

Table 4.2a is a summary of the included study Thior (2006). It was conducted in Botswana with an aim of detecting the differences between EBF and EFF under ARV prophylaxis. The outcomes were HIV infection, infant mortality and HIV-free survival.

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Table 4.2b: Risk of bias table Thior (2006)

DOMAIN/ QUESTION	LOW RISK	HIGH RISK	UNCLEAR	DESCRIPTION
Sequence generation?	√			1200 HIV pregnant women were randomly assigned to exclusive breastfeeding and exclusive breastfeeding during enrolment at 34 weeks gestation
Allocation concealment?	√			Centralised or pharmacy-controlled trial
Blinding of participants, personnel and outcome assessor?	√			Despite study participants and researchers being unaware of the feeding options until 34 weeks gestation, after that it was impossible to blind the participants. It is unclear whether outcome assessors were unblinded
Incomplete outcome data adequately addressed?	√			Data assessments were made for each main outcome: HIV infection, infant mortality and HIV-free survival. Intention to treat analysis was done. All the 1079 enrolled infants were included in the analysis despite the loss to follow up. The loss of follow up was generally less than 15%. In the breastfeeding arm it was 4.3% and 9.0% while in the exclusive breastfeeding arm it was 2.7% and 9.0% at 7 and 18 months age
Study free of selective outcome reporting?	√			There was no evidence of reporting of only desirable results
Free of other bias?	√			Generally there were no other signs of any biases in the study

Quality assessment was performed for the included study, Thior (2006). The risk of bias was low. It was a study of good methodological design and suitable for meta-analysis.

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Table 4.3a: Characteristics of included study: Nduati (2000)

Methods	Randomised controlled trial
Participants	425 HIV-1 seropositive, antiretroviral-naive pregnant women at 32 weeks were enrolled into two arms. 212 were assigned to exclusive breastfeeding and 213 for exclusive formula feeding arm. From the exclusive breastfeeding arm, 15 babies were lost due to miscarriages, maternal death, loss to follow up before delivery and stillbirths before delivery resulting in 197 live new born singletons. In the exclusive formula feeding arm, 9 were lost due to the above mentioned reasons resulting in 204 live singletons and first twins. A total of 401 were included in the analysis
Interventions	Exclusive breastfeeding and exclusive formula feeding both without infant prophylaxis, only maternal HAART
Comparisons	Exclusive breastfeeding vs. Exclusive formula feeding
Outcomes	Infant HIV infection, infant mortality and HIV-free survival
Timeline	Outcomes measured at 6 and 24 months

Table 4.3a summarises a study by Nduati (2000). This randomised controlled trial conducted in Rwanda compared exclusive breastfeeding versus exclusive formula feeding. The total number of infants included in the analysis was 401. The outcomes were HIV infection, Infant mortality and HIV-free survival measured at 6 and 24 months.

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Table 4.3b Risk of bias table: Nduati (2000)

DOMAIN/ QUESTION	LOW RISK	HIGH RISK	UNCLEAR	DESCRIPTION
Sequence generation?	√			The randomisation method was used
Allocation concealment?	√			Computer generated allocation to either exclusive breastfeeding or exclusive formula feeding
Blinding of participants, personnel and outcome assessor?	√			Study participants and researchers were unaware of the feeding options until 32 weeks gestation, after that it was impossible to blind the participants. It is unclear whether researchers and outcome assessors were unblinded
Incomplete outcome data adequately addressed?	√			Data assessments were made for each main outcomes; HIV infection and infant mortality. Intention to treat analysis was done. The loss to follow up after delivery was 6.0% and then a total of 17% over two years and were all included in the analysis
Study free of selective outcome reporting?	√			There was no evidence of reporting bias or reporting of only desirable results
Free of other bias?	√			Generally there were no other signs of any biases in the study

The risk of bias was performed for methodological quality for the included study Nduati (2000) as shown by table 4.2b. The results indicated that the study had few methodological flaws and bias. It was therefore suitable to be used for meta-analysis.

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Table 4.4a Characteristics of included study: Peltier (2009)

Methods	Non randomised interventional Cohort study
Participants	562 HIV positive pregnant women were enrolled into the study. 240 chose breastfeeding with HAART and 322 chose formula feeding. There were 551 deliveries of which 5 died from before two days and 14 were stillbirths. 532 infants were then enrolled; 227 on breastfeeding and 305 on the formula feeding arm
Interventions	Exclusive breastfeeding with maternal HAART and formula feeding
Comparisons	Exclusive breastfeeding vs. Exclusive formula feeding
Outcomes	Infant HIV infection, infant mortality and HIV-free survival
Timeline	Outcomes measured at 9 months

Table 4.4a is a detailed summary of the included study conducted in Kenya by Peltier (2009). The non-randomised Interventional cohort study enrolled 562 pregnant women who chose infant feeding options for themselves. 532 infants were included in the study and the outcomes measured at 9 months of age were infant HIV infection, infant mortality and HIV-free survival.

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4.4b Risk of bias table: Peltier (2009)

DOMAIN/ QUESTION	LOW RISK	HIGH RISK	UNCLEAR	DESCRIPTION
Sequence generation?		√		Non randomised intervention cohort study
Allocation concealment?		√		Patients chose their own suitable infant feeding option
Blinding of participants, personnel and outcome assessor?		√		No blinding was done to both the participants and personnel. It is unclear whether outcome assessors were blinded or not
Incomplete outcome data adequately addressed?	√			Intention to treat analysis was done and all the outcome data was assessed. There were 15 infants lost to follow up from the exclusive breastfeeding arm and 3 from the exclusive formula feeding arm, thus 3.4% loss
Study free of selective outcome reporting?	√			There was no evidence of reporting only positive results
Free of other bias?	√			There are no other signs of any biases in the study

The risk of bias table for methodological quality assessment was performed for the included study by Peltier (2009). The study had fairly good methodological quality. Randomisation, allocation concealment and blinding were impossible because of the study design (cohort study).

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4.2.2.2 Excluded studies

Table 4.5 Characteristics of excluded studies

Study ID	Reasons for exclusion
1. Bedri (2008) 2. Dabis (1999) 3. Kumwenda (2008) 4. Lehman (2008) 5. Kilewo (2008) 6. Guay (1999) 7. Violari (2008) 8. Homsy (2010)	Primary objectives, intervention and comparison were different from the researcher's as stated in the protocol. In all the studies, trialists' aims were to test the efficacy of antiretroviral therapies in two exclusive breastfeeding arms. They compared exclusive breastfeeding, plus an antiretroviral vs. exclusive breastfeeding with an extended dose antiretroviral or a different antiretroviral. The antiretroviral therapies varied across the studies, duration or timing of therapy. Despite this, all the studies had the same outcomes as the review's, HIV infection
9. Iliff (2005)	It was a sub-study of another trial which gave HIV positive breastfeeding women vitamin A after delivery. The aim was to find out the impact of it on maternal and neonatal outcomes; the intervention was different from that of the review
10. Coovadia (2007)	The study had high risk of bias Sequence generation - NO Allocation concealment - NO Blinding - NO Intention to treat analysis - NO, available case analysis was done Loss of follow up - The study had 26 % loss to follow up Free of other sources of bias – YES
11. Becquet (2009)	The study outcomes were irrelevant for this review. The methodology was also irrelevant; it was a pooled data from 2 cohort studies.

Table 4.5 is a summary of 11 articles that were excluded from the review analysis. These studies were eliminated due to various reasons as indicated in the table. The independent reviewers (AP) and (OK) individually assessed the studies and (KH) was consulted for consensus regarding the decision to exclude Coovadia (2007).

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4.3 RISK OF BIAS IN INCLUDED STUDIES

Table 4.6: Risk of bias graph: review of authors' judgments about each risk of bias item presented as percentages across all included studies

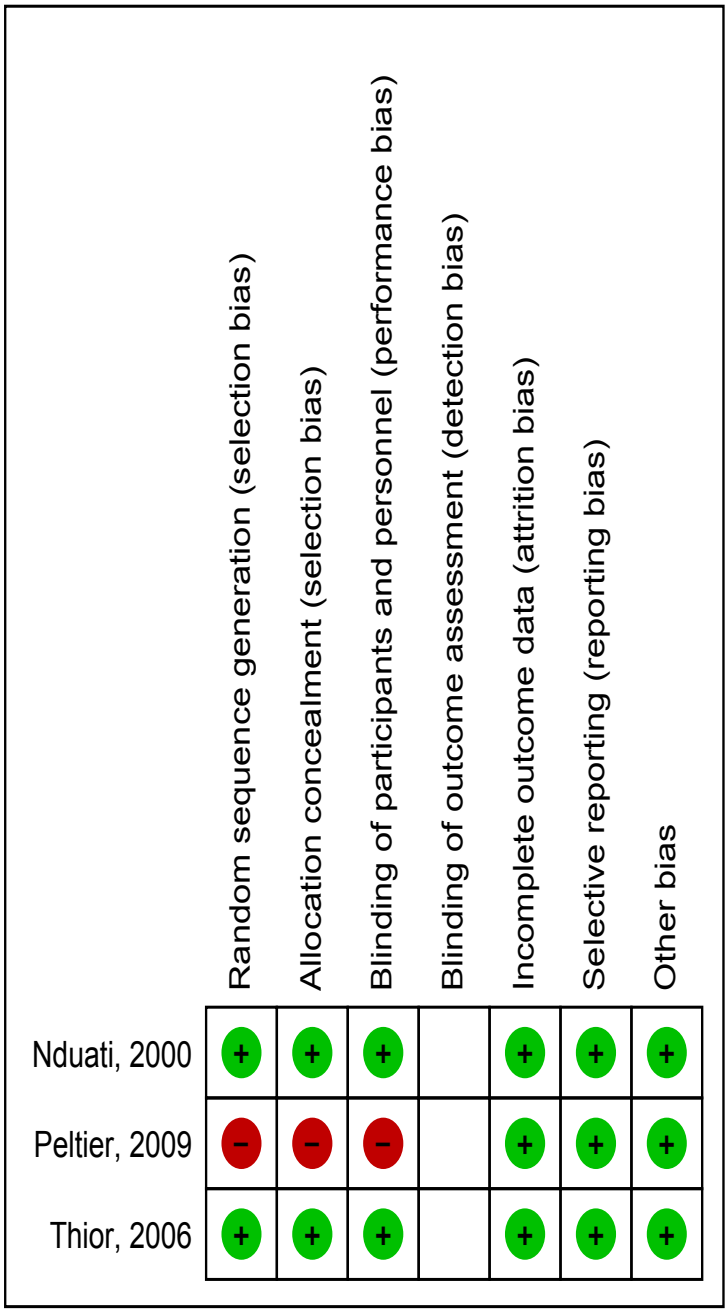

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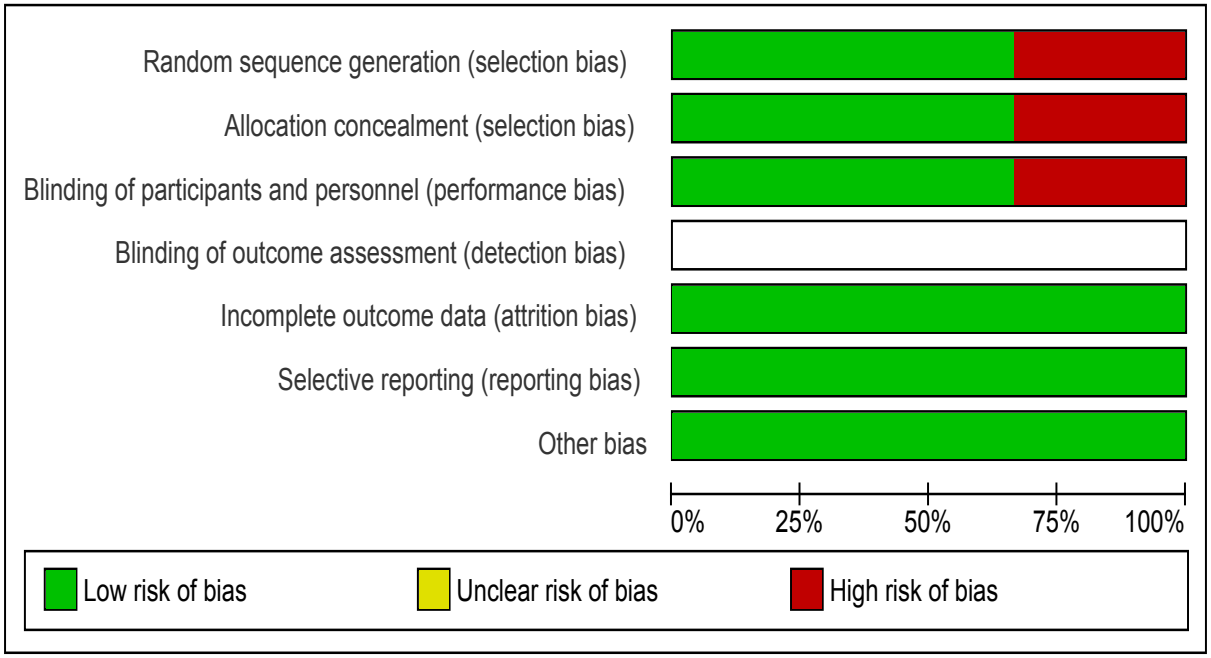
Table 4.7: Risk of bias summary: review of authors' judgments about each risk of bias item for each included study



4.3.1 Randomisation

Randomisation was confirmed in 2/3 articles; Thior (2006) and Nduati (2000), were considered low risk. Peltier (2009), conducted a good quality interventional cohort study but since no method of randomisation was used, a judgement of high risk was given.

4.3.2 Allocation (selection bias)

Allocation concealment was confirmed in 2/3 articles; Thior (2006) and Nduati (2000). A judgement of low risk was used. Patients chose their interventional method in Peltier (2009), therefore, a judgement for high risk was used.

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4.3.3 Blinding (performance bias and detection bias)

Blinding was confirmed as low risk in 2/3 articles: Thior (2006) and Nduati (2000). Despite study participants and researchers being unaware of the feeding options until 34 and 32 and weeks gestation, after that it was impossible to blind the participants. It is unclear whether the outcome assessors were blinded. Therefore, a judgement of unclear of bias was used. In Peltier (2009), no blinding was done to both the participants and personnel, it was then considered unclear of whether outcome assessors were blinded or not.

4.3.4 Incomplete outcome data (attrition bias)

A judgement of low risk was confirmed in 3/3 articles included in the study. Intention to treat analysis was done in all the trials. The participants were analysed according to the intervention they were allocated to regardless of whether they completed it or not.

4.3.5 Selective reporting (reporting bias)

According to Higgins and Green (2006:152), reporting bias entails a tendency to under-report undesirable results or outcomes. The reviewer did not identify any reporting bias in the included studies. A judgement of low risk was confirmed in 3/3 articles included in the study for no risk of reporting bias.

4.3.6 Other potential sources of bias

Generally there were no other signs of any biases in all the 3 studies. A judgement of low risk was confirmed for ‘free of other sources of bias?’ (low risk). `

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4.4 EFFECTS OF INTERVENTIONS

4.4.1 HIV infection

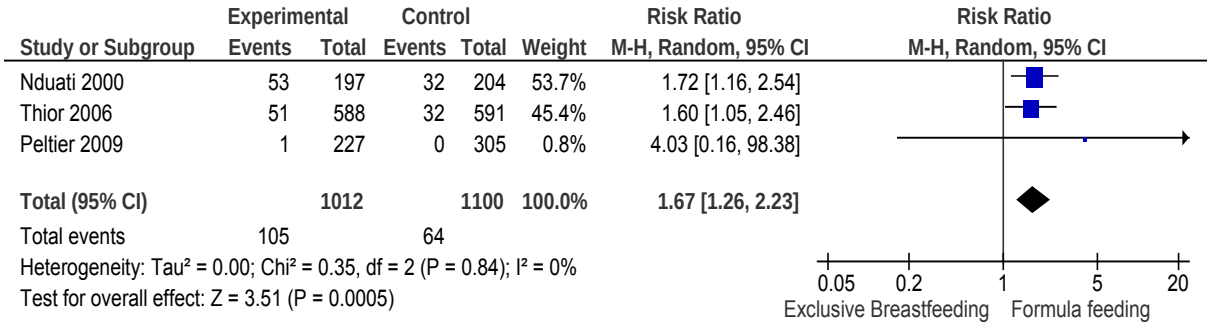

Figure 4.1: Exclusive breastfeeding vs. Exclusive formula feeding as measured at 6, 7 and 9 months of age. Outcome: HIV infection

Figure 4.1 illustrates the HIV infection rate among the three studies included with a total of 2112 infants. The studies reported outcomes at 6, 7 and 9 months. In all the included studies, mothers exclusively breastfed for 6 months. Exclusive breastfeeding was associated with a higher HIV transmission rate (RR 1.67, 95% CI, 1.26-2.23, p=0.0005). The probability of HIV infection in exclusive breastfeeding was 1.67 times higher than compared to the exclusive formula feeding arm. The heterogeneity between the three studies was rated not important (Chi²= 0.35, p=0.84, I²=0%).

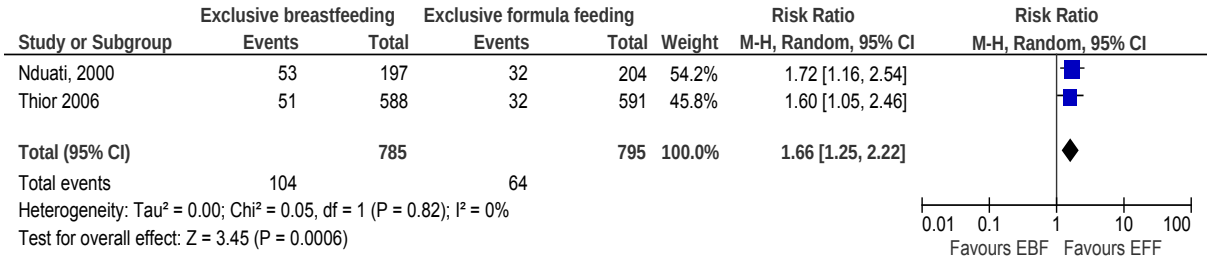

Figure 4.2: Sensitivity analysis: Exclusive breastfeeding for 6 months vs. Exclusive formula feeding as measured at 6 and 7 months of age. Outcome: HIV infection

The results of sensitivity in figure 4.2 indicated no significant change when compared to the results of figure 4.2. Two studies by Nduati (2000) and Thior (2006), (n=1580) undeniably showed that exclusive breastfeeding is associated with a HIV infection rate (RR 1.66, 95%

CI, 1.25-2.22, p=0.0006). The heterogeneity between the three studies was rated as not important (Chi²= 0.05, p=0.82, I²=0 %).

4.4.2 Infant mortality

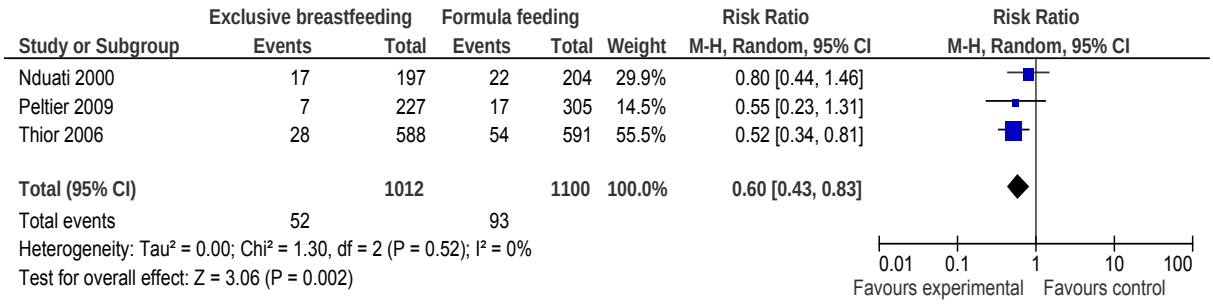

Figure 4.3: Exclusive breastfeeding for 6 months vs. Exclusive formula feeding as measured at 6, 7 and 9 months of age. Outcome: Infant mortality

The three trials included in the analysis provided dichotomous data on infant mortality. When the data was meta-analysed, it indicated that the outcomes favoured exclusive breastfeeding and are associated with a low mortality rate as compared to exclusive breastfeeding (RR 0.60, 95% CI, 0.43-0.83, p=0.002). Heterogeneity was not of concern in the study (Chi²= 1.30, p=0.52, I²=0%).

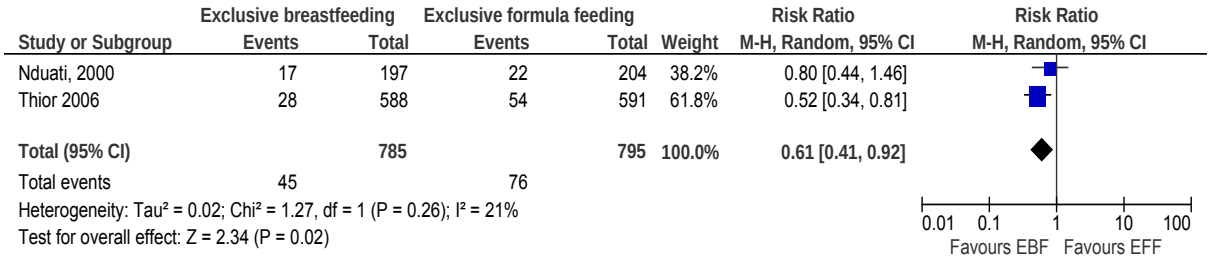

Figure 4.4: Sensitivity analysis: Exclusive breastfeeding for 6 months vs. Exclusive formula feeding as measured at 6 and 7 months of age. Outcome: Infant mortality

Sensitivity analysis of two trials (n=1580) with outcomes measured at 6 and 7 months had statistically significant results of a 95% CI, 0.41- 0.92, p=0.02, RR 0. 61). Statistical heterogeneity (Chi²=1.27, p=0.26, I²=21%) was deemed unimportant. This re-analysis did not materially change the results in figure 4.3, hence strengthening the confidence that can be placed in the results (Deeks et al., 2006:151).

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4.4.3 HIV-free survival

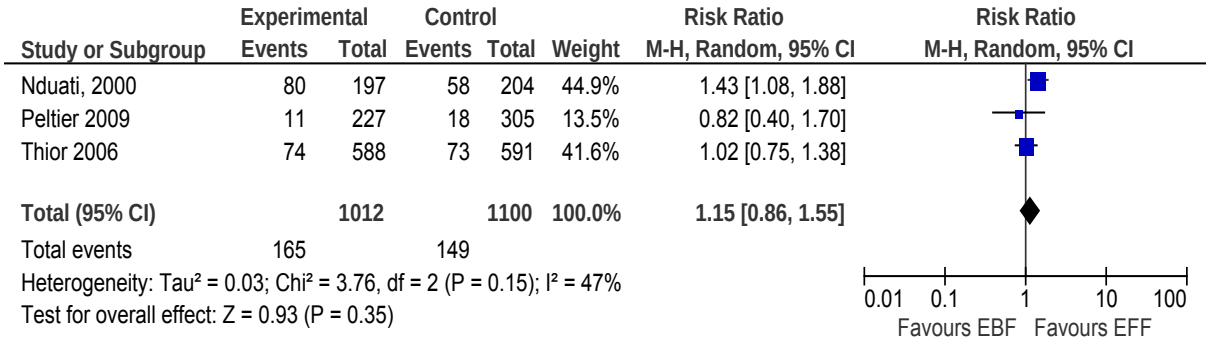

Figure 4.5: Exclusive breastfeeding for 6 months vs. Exclusive formula feeding as measured at 7, 9 and 24 months of age. Outcome: HIV-free survival

A pooled analysis of three trials (n=2112) provided dichotomous data on HIV-free survival. There was a non-significant tendency towards longer HIV-free survival in the exclusive formula feeding group in comparison to exclusive breastfeeding (RR 1.15, 95% CI, 0.86-1.55, p=0.35). The level of statistical heterogeneity was considered moderate (Chi^2=3.76, p=0.15, I^2=47%).

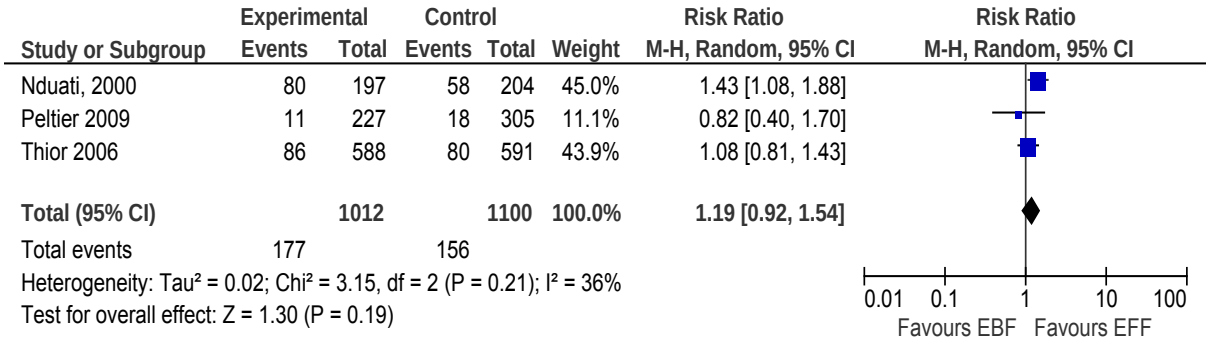

Figure 4.6: Overall sensitivity analysis: Exclusive breastfeeding for 6 months vs. Exclusive formula feeding as measured at 9, 18 and 24 months. Outcome: HIV-free survival

Sensitivity analysis was performed on the same three trials (n=2112) with outcomes measured at different intervals to those of figure 4.8. The results still indicated that exclusive formula feeding did not significantly change the duration of HIV-free survival (RR 1.19, 95%

CI, 0.92-1.54, p=0.19). The heterogeneity between the three studies was rated not important (Chi²= 3.15, p=0.21, I²=36 %).

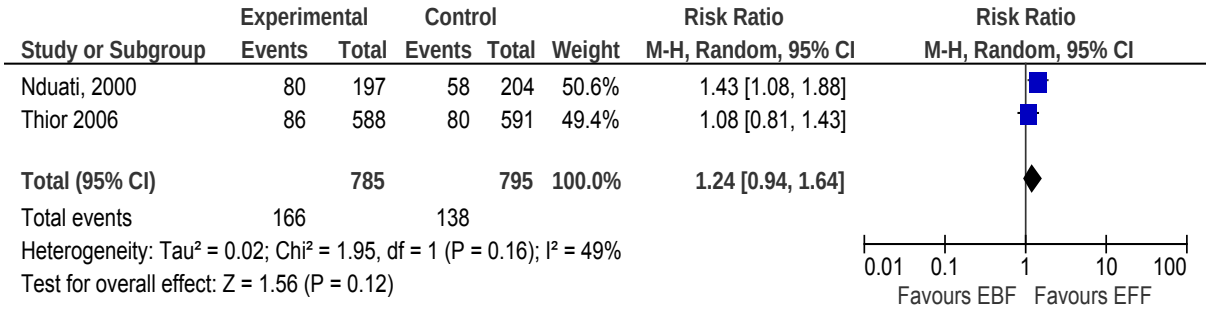

Figure 4.7: Sensitivity analysis: exclusive breastfeeding for 6 months vs. Exclusive formula feeding as measured at 18 and 24 months. Outcome: HIV-free survival

A second sensitivity analysis was done on two trials (n=1580) with dichotomous data on HIV-free survival measured at 18 and 24 months. The results still had a non-significant tendency towards a longer HIV-free survival in the exclusive formula feeding (RR 1.24, 95% CI, 0.94-1.64, p=0.12). The level of statistical heterogeneity was moderate (Chi²=1.95, p=0.16, I²=49%).

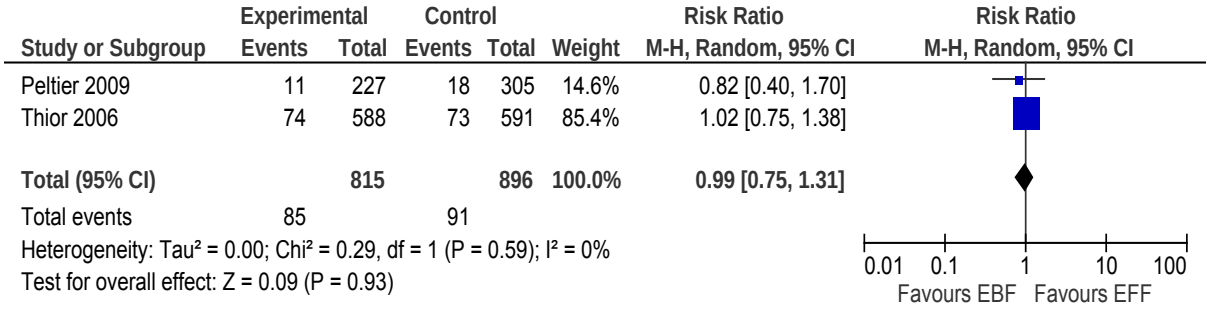

Figure 4.8: Sensitivity analysis exclusive breastfeeding for 6 months vs. Exclusive formula feeding as measured at 7 and 9 months. Outcome: HIV-free survival

The last sensitivity analysis on two trials (n=1711) measuring HIV-free survival at 7 and 9 months showed no evidence of a difference in outcomes between the two groups at 6 and 7 months (RR 0.99, 95% CI, 0.75-1.31, p=0.93). Statistical heterogeneity was confirmed unimportant (Chi²=0.29, p=0.59, I²=0%).

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4.5 CONCLUSION

Chapter 4 focused on the analysis of the data. The results indicated that exclusive breastfeeding is associated with HIV infection from mother to child as compared to exclusive formula feeding but this intervention is associated with high mortality rate. The result showed no statistically differences in HIV free survival between the two interventions.

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CHAPTER 5

DISCUSSION

5.1 INTRODUCTION

This section provides a discussion of the results in chapter 4 to provide meaningful explanations to the data analysed in relation to the objectives of the review. The study's main objective was to evaluate the evidence on exclusive breastfeeding versus formula feeding and/ or mixed feeding with the use of antiretroviral prophylaxis in the prevention of HIV-1 transmission from mother to child. It then, finally either accepts or rejects the hypothesis: exclusive breastfeeding is effective in the prevention of HIV-1 transmission from mother to child.

5.2 DISCUSSION

5.2.1 HIV infection

The review found that the rate of HIV infection is higher in exclusive breastfeeding when compared to formula feeding (RR 1.26, 95%CI, 1.26-2.23, p=0.0005). The studies included in the analysis reported a good compliance rate in both feeding methods which have been found to have a significant impact on the transmission rate (Chapter 2: 2.2- 2.3). Sensitivity analysis was incorporated due to the fact that HIV infection was measured at different intervals across studies. It confirmed the results that exclusive breastfeeding was associated with higher HIV infection rates as compared to exclusive formula feeding. There was no evidence of statistical heterogeneity. Recently, a systematic review of six trials on interventions for preventing late postnatal mother-to-child transmission of HIV concluded that complete avoidance of breastfeeding is efficacious in preventing MTCT of HIV (Horvath et al., 2010:2). In addition, if breastfeeding is initiated, a combination of two interventions is essential, that is exclusive breastfeeding during the first few months of life and extended antiretroviral prophylaxis (Horvath et al., 2010:2). The included studies had participants' breastfeeding exclusively for six months with HIV prophylaxis for infants or maternal HAART of which none was extended. None of the included studies compared exclusive breastfeeding with mixed feeding. An interventional cohort study conducted in Durban, South Africa found that infants who were mixed fed had significantly high rates of acquisition

of MTCT of HIV and were 11 times at risk (HR (hazard ratio) 10.87, 95% CI 1.51-78.00, p=0.018) (Coovadia et al., 2007:1107).

In some studies, exclusive breastfeeding has been associated with a lower risk of postnatal transmission of HIV as compared to non-exclusive breastfeeding, that is, breastfeeding with formula, other fluids (water, fruit juice) or solids (baby food) (Leroy 2001:15; Iliff et al., 2005:699). The introduction of solid foods or animal milk to breastfeeding infants born to HIV positive mothers before the age of 3 months was associated with a fourfold greater risk of postnatal transmission at 6 months compared with exclusive breastfeeding (Iliff et al., 2005:703). The overall result of this review and that which Horvath (2010) favours is complete avoidance of breastfeeding.

5.2.2 Infant mortality

The results of this meta-analysis indicated that exclusive breastfeeding is associated with a lower infant mortality rate as compared to exclusive formula feeding (RR 0.60, 95% CI, 0.43-0.83, p=0.002 , sensitivity analysis on outcome measured between 6 and 7 months, 95% CI, 0.41- 0.92, p=0.02, RR 0.61). There was no evidence of statistical heterogeneity in the results (Chi^2=1.30, p=0.52, I^2=0%) and (Chi^2=1.27, p=0.26, I^2=21%). Each of the included studies individually reported lower infant mortality rates as compared to exclusive formula feeding. Horvath et al., (2010:2) supported this finding stating/saying that despite exclusive formula feeding being efficacious in preventing MTCT of HIV, it is associated with mortality (e.g., diarrhoeal morbidity if formula is prepared without clean water). Coovadia et al., (2007:1107) had the same findings; the study showed that mortality rate is lower in exclusive breastfed infants as compared to exclusively formula fed infants. The cumulative 3 month mortality in exclusively breastfed infants was 6.1% versus 15.1% in infants given replacement feeds.

5.2.3 HIV-free survival

The review found that exclusive breastfeeding is not associated with longer HIV-free survival, when outcomes were measured at 7, 9 and 24 months (RR 1.15, 95% CI, 0.86-1.55, p=0.35). The sensitivity analysis was performed on the same three trials (n=2112) with outcomes measured at 9, 18 and 24 months. The results still indicated that exclusive breastfeeding was not associated with an increase in HIV-free survival (RR 1.19, 95% CI, 0.92-1.54, p=0.19). Even if there was heterogeneity between the three studies, it was rated

as not important (Chi²= 3.15, p=0.21, I²=36 %). The performed sensitivity analyses where outcomes were measured at 18 and 24 months (Nduati, 2000; Thior, 2006) or at 7 and 9 months (Peltier, 2009; Thior, 2006) did not yield any different findings.

Two individual studies Peltier (2009) and Thior (2006), that were included in the meta-analysis reported the same findings as in this review, while Nduati (2000), reported a significant lower HIV-free survival in the breastfeeding arm. According to the review, exclusive breastfeeding is not associated with a longer HIV-free survival.

5.3 OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

The following research question was used as a guide before initiation of the review: Is exclusive breastfeeding effective in the prevention of HIV-1 transmission of Mother to Child? The reviewer conducted an extensive literature search to identify all literature and studies related to the review.

The included studies contributed and addressed exclusive breastfeeding and its effectiveness in the prevention of HIV-1 transmission from Mother to Child. They compared exclusive breastfeeding to exclusive formula feeding. None of the studies compared exclusive formula feeding with mixed feeding. In daily practice, mixed feeding is discouraged due to its association with high transmission rate of HIV-1. It would be unethical for trialists to randomly assign patients to mixed feeding. Though some patients did not completely adhere and comply with either exclusive breastfeeding or formula feeding, the investigators did not report the results as mixed feeding. Exclusive formula feeding is associated with a 0% HIV-1 transmission rate. Therefore, this might disturb the completeness of the evidence.

Despite this, HIV infection, infant mortality and HIV-free survival were addressed. The studies were conducted in developing countries in semi-rural and in cities. These multi-centred results increase the generalisability. They can be applied in a number of settings, that is, the evidence can be transferred to different areas.

In some developing countries, especially Botswana and South Africa, the government provides free formula feeding to infants. These mothers need intensive training on how to make the feeding option safe (clean preparation) since it is associated with high mortality from infections such as diarrhoea, respiratory and ear infections. A mother who chooses to breastfeed must be encouraged to do it exclusively during the first 4-6 months. One of the excluded studies, Coovadia et al., (2007), conducted a study in South Africa. It was found

that mixed feeding was associated with high HIV- transmission as compared to the other feeding options. Evidence on HIV-free survival could not show any promise that exclusive breastfeeding could be associated with a longer HIV-free survival period.

5.4 QUALITY OF EVIDENCE

The review consists of two randomised and one cohort study. The RCTs are mostly of good quality. Randomised controlled studies are considered as the best designs in addressing research questions regarding effectiveness of therapeutic interventions (Higgins & Green, 2006:60). They are characterised by selection criteria, random sampling, control, blinding procedures, intervention protocol, intention to treat, effect size and sometimes crossover designs (Brink et al., 2008:96). These characteristics decrease the risk of bias in studies. All the included studies had a control group (exclusive formula feeding). The control group was used as a comparison to observe and evaluate the effects of exclusive breastfeeding.

Cohort studies can be included in systematic reviews. Peltier (2009), did not randomly assign subjects to an intervention; the participants chose their feeding options. This is important as sometimes participants fail to adhere and comply with the randomly assigned infant feeding option, due to socio-economic barriers. Peltier (2009), reported a lower rate of HIV-1 transmission from mother to child measured at 9 months (1 infant in exclusive breastfeeding and none in exclusive formula feeding) as compared to other studies.

In this review a methodological quality assessment tool 'risk of bias table' was used to assess studies individually for quality. The two randomised controlled studies had allocation concealment, however, blinding was unclear in both. The three studies reported attrition bias between 3.4%-17%. Intention to treat analysis was confirmed in 3/3 articles. None of the included studies had evidence of selective (reporting) bias. Other sources of bias were not found in any of the articles.

5.5 POTENTIAL BIASES IN THE REVIEW PROCESS

During the review process, measures were taken to minimise the risk of bias. The same research question was used as a guide and it remained consistent throughout. The reviewer was cautious not to modify it.

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An extensive literature search was conducted across a wide range of databases. The main purpose was to retrieve as many articles as possible and to avoid excluding important studies, thus eliminating selection bias.

Quality assessment was performed using standardised data extraction tools from the Cochrane collaboration. Two independent reviewers, (AP) and (OK) independently assessed the methodological quality. They determined which study met the inclusion criteria. Disagreements were solved by discussion, a third reviewer (KH) was contacted for further consultations. Prof. Hofmeyr, an expert in systematic reviews and editor of Cochrane collaboration group for systematic reviews, was contacted repeatedly during quality assessments. The risk of bias was minimised by following these procedures.

5.6 AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES

Generally, the results of the review do not vary from what other reviewers have found. A systematic review by Horvath et al., (2010) concluded that complete avoidance of breastfeeding is efficacious in preventing MTCT, but it is associated with significant higher infant mortality. Exclusive breastfeeding with extended antiretroviral prophylaxis can minimise the chances of MTCT. The review did not focus on breastfeeding and extended antiretroviral prophylaxis. Some excluded studies on standard antiretroviral versus extended antiretroviral prophylaxis and exclusive breastfeeding reported lower MTCT in the extended antiretroviral arm (Bedri, 2008; Dabis, 1999; Kumwenda, 2008;, Lehman, 2008; Kilewo, 2008; Guay, 1999; Violari, 2008; and Homsy, 2010).

Two of the included studies individually reported the same finding as in this review, while one reported a lower HIV-free survival among exclusive breast-fed infants.

5.7 CONCLUSIONS ON THE TWO INTERVENTIONS

5.7.1 Exclusive breastfeeding

The results of the review have shown the risks and benefits of exclusive breastfeeding. The trialists of the included studies reported less than 100% compliance or adherence to exclusive breastfeeding by study participants, respectively. The results showed a significant higher HIV transmission in the breast-fed infants, and they did not show any evidence that exclusive breastfeeding could be associated with a longer HIV-free survival as reported by

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the individual studies. According to the findings, mortality is reduced through exclusive breastfeeding.

5.7.2 Exclusive Formula feeding

According to the literature, exclusive formula feeding carries a 0% rate of HIV transmission. The findings of the review indicated a significant benefit of choosing EFF as an infant feeding option for the prevention of HIV-1 transmission. However, in included studies, HIV infection rates under exclusive formula feeding were reported, this could be an indicator of mixed feeding and poor adherence. EFF is also a major risk factor of mortality in infants.

5.8 RECOMMENDATIONS

5.8.1 Excusive breastfeeding

There is a need for larger prospective, multi-centred RCTs of good methodological quality on exclusive breastfeeding to obtain more evidence based results. Health care workers and policy makers play a major role in the welfare of the population. It is critical that if the AFASS criterion of EFF is not met, exclusive breastfeeding should be encouraged. Some mothers opt for breastfeeding as a personal choice and this shouldn't hinder the health care workers from supporting and encouraging them to adhere completely to this feeding option. The use of antiretroviral prophylaxis as prescribed should also be emphasized. This has shown to lessen the chances of MTCT. Studies have also shown that extended antiretroviral therapy decreases MTCT of HIV. Currently, the national regime of antiretroviral therapy in breastfeeding is not extended, policy makers could review this and consider if it is not feasible in the current state.

There are several challenges regarding the promotion of exclusive breastfeeding especially in HIV positive mothers. Socio-cultural barriers play a major role. Health care workers and public health policy makers can aim at attending everyone at a community level. Several programmes such as the South African-based non government organisation; Mothers to Mothers and community breastfeeding counsellors should be expanded and aim at doing home visits, organising health education workshops at community level. Home or family visits may also help individual family members to get more clarity and understanding. These programmes should encourage the entire community, convince them to involve themselves in issues regarding HIV and breastfeeding especially before large scaled studies can be done because these factors hinder research and daily evidence based practice.

HIV activists' programmes aims at supporting those infected and affected using personal experience. There is a need in the community to have such people especially those who opted for exclusive breastfeeding with an HIV positive status. Such people may bring hope, encouragement and support to these HIV positive mothers. The health care workers should assist in facilitation of these programmes to make them feasible.

5.8.2 Exclusive formula feeding

An exclusive formula feeding option has shown promise on the effectiveness of preventing HIV-1 transmission from mother to child. However, it is associated with higher infant mortality. Literature has shown that EFF can be considered in circumstances where it is sustainable, safe, affordable, accessible and feasible. The government policies need to be reinforced to improve socio-economic conditions of the people. Due to poor housing, water, sanitation, access to health facilities in a large number of HIV populations, the AFASS criteria cannot be met. Therefore there is a need in such situations to promote excusive breastfeeding and antiretroviral adherence thus discouraging exclusive formula feeding. However, if AFASS criterion is met, health care providers and decision makers need to promote EFF and educate how to prepare, store and to give formula milk in a safe way. Community and individual family involvement is necessary to overcome socio-cultural barriers.

In all instances, mixed feeding should be discouraged due to its risks of high HIV transmission and mortality rates. Large multicentre RCTs of appropriate methodological quality on a safe feeding option in the prevention of MTCT transmission HIV-1 should be conducted to provide more evidence.

5.9 CONCLUSION

Infant feeding choices in HIV exposed infants have become a tremendous challenge especially in the developing countries. The population is not well informed due to illiteracy and there is poor access to basic health services. Mostly, cultural backgrounds play a major role in decision making regarding safe infant feeding guidelines and unfortunately this affects the well-being of the infants. The reviewer discussed, concluded the research findings and made suggestions based on the results. These results inform practice and ideas were given on how to expand the existing body of knowledge such as the conducting of multi-centred, RCTS of appropriate methodological quality.

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ANNEXURES

ANNEXURE I. – Data extraction forms

Data extraction form; Nduati, 2000.

1. Source

Study ID	01
Reviewer	Angel Phuti; Oswell Khondowe
Author & year	Nduati, R., John, G., Mbori-Ngacha, D., Richardson, B., Overbaugh, J., Mwatha, A., Ndinya-Achola, J., Bwayo, J., Onyango, F. E., Hughes, J. & Kreiss, J.
Journal	2000: *JAMA,* 283**,** 1167-74.
Title	Effect of Breastfeeding and formula on transmission of HIV-1: A randomised Clinical trial.
Country	Nairobi-Kenya

2. Eligibility criteria

(Indicate with a cross the appropriate one)

2.1 Types of studies

Randomised Controlled Trial	X
Quasi-experimental	
Cohort study	
Published data	X
Unclear/NO	

2.2 Types of participants

HIV exposed babies born from HIV-1 positive mothers.	X
Unclear/NO	

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2.3 Types of interventions

Exclusive Breastfeeding vs. Formula feeding under a certain antiretroviral	X
Exclusive breastfeeding vs. Mixed feeding under a certain antiretroviral.	
Unclear/NO.	

2.4 Types of outcomes

HIV infection	X
Infant mortality	X
HIV free survival	X
Unclear/NO	

If any of the above answers are 'NO', do not proceed. If study is to be included in 'Excluded studies' of the review, record the information into 'the table of excluded studies'.

2.6 Lost to follow up <20%

Equation	YES X	NO

2.6.1 Reasons for loss to follow up

Reasons for attrition included: maternal death, loss to follow up/ not returning to study site.

2.6.2 Other reasons for exclusion

None

3. Methodology

3.1 Study design

RCT	X

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Quasi-experimental	
Cohort	

3.2 Study duration

Month & Year	November 1992 – July 1998

3.3 Eligibility criteria

Participant: HIV exposed infants whose mothers who are HIV-1 positive
Intervention: Exclusive breastfeeding (with antiretroviral)
Comparison: Exclusive formula feeding
Outcomes: HIV infection, mortality
Measured at 6,18 & 24 months

3.4 Cochrane Collaboration 'Risk of Bias' Tool: Methodological quality/ Risk of bias assessment. Each question or domain should be answered with either; 'LOW RISK' or 'HIGH RISK' or 'UNCLEAR'.

DOMAIN/QUESTION	JUDGEMENT	DESCRIPTION
Sequence generation?	Low risk	Randomisation method was used.
Allocation concealment?	Low risk	Computer generation
Blinding of participants, personnel and outcome assessor?	Low risk and Unclear for outcome assessors	At 32 weeks until delivery the participants were unblinded after that, it was impossible to blind.
Incomplete outcome data adequately addressed?	Low risk	Intention to treat analysis was done.
Study free of selective outcome reporting?	Low risk	-
Free of other bias?	Low risk	-

3.5 Participants

Sample size	425 mothers who gave birth to 401 infants
Total number included in the analysis	401
Age during initiation of intervention	Immediately after delivery
Sex	Female and male
Diagnostic criteria for HIV	Enzyme linked Immuno-absorbent assay
Setting	Nairobi; Kenya
Socio-demographic	Low socio economic status
Country	Kenya
Date of study	November 1992- July 1998

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3.6 Interventions

Experimental group with or without antiretroviral	
Type	**Duration**
EBF	6 months
Control group with or without antiretroviral	
Type	**Duration**
EFF	6

3.7 Outcome measures as stated in the review

(Tick appropriate box)

1. HIV infection	YES X	NO
2. Infant mortality	YES X	NO
3. HIV free survival	YES X	NO

3.8 Outcomes definitions

1. HIV infection:	HIV positive through the use of ELISA test
2. Infant mortality:	Death
3. HIV free survival:	HIV infection and death

4. Results

Number of Patients:		
	Randomised or allocation	**Analysed**
Experimental	197	197
Control	204	204
Total	401	401(The total number that remained after delivery)

4.1 Summary data for each intervention group (at 6 months)

1. HIV infection	**Event**	**No event**	**Total**
Experimental group	53	159	197
Control group	32	181	204

(Measured at 6 months)

2. Infant mortality	**Event**	**No event**	**Total**
Experimental group	17	180	187
Control group	22	182	204

(Measured at 24 months)

3.HIV free survival	**Event**	**No event**	**Total**
Experimental group	80	117	197
Control group	58	146	204

4.2 Continuous data

Outcome	Experimental group (mean±SD)	Control group (mean±SD)	WMD	CI 95%	P- value

4.3 Estimate of effect with confidence interval/ P-value

1. HIV infection	RR	CI 95%	P-value
Experimental group			
Control group			

1. Infant mortality	RR	CI 95%	P-value
Experimental group			
Control group			

1. HIV free survival	RR	CI 95%	P-value
Experimental group			
Control group			

4.4 Subgroup analysis

Outcomes measured at different age (month)

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4.5 Miscellaneous

Key conclusions	The frequency of HIV-1 was 16.2% in this randomised clinical trial, and the majority of infections occurred during breastfeeding. The use of breastmilk substitutes prevented 44% of infant infections and was associated with improved HIV- free survival.
Other significant comments from authors	-
References to other relevant trials	X
More information required	-
Others:	

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Data extraction form; Thior, 2006.

1. Source

Study ID	02
Reviewer	Angel Phuti and Oswell Khondowe
Author & year	Thior, I., Lockman, S., Smeaton, L. M., Shapiro, R. L., Wester, C., Heymann, S. J., Gilbert, P. B., Stevens, L., Peter, T., Kim, S., Van Widenfelt, E., Moffat, C., Ndase, P., Arimi, P., Kebaabetswe, P., Mazonde, P., Makhema, J., Mcintosh, K., Novitsky, V., Lee, T. H., Marlink, R., Lagakos, S. & Essex, M. 2006
Journal	*JAMA,* 296**,** 794-805.
Title	Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study.
Country	Botswana

2. Eligibility criteria

(Indicate with a cross the appropriate one)

2.1 Types of studies

Randomised Controlled Trial	X
Quasi-experimental	
Cohort study	
Published data	X
Unclear/NO	

2.2 Types of participants

HIV exposed babies born from HIV positive mothers.	X
Unclear/NO	

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2.3 Types of interventions

Exclusive Breastfeeding vs. Formula feeding under a certain antiretroviral or not.	X
Exclusive breastfeeding vs. Mixed feeding under a certain antiretroviral or not.	
Unclear/NO.	

2.4 Types of outcomes

HIV infection	X
Infant mortality	X
HIV free survival	X
Unclear/NO	

If any of the above answers are 'NO', do not proceed. If study is to be included in 'Excluded studies' of the review, record the information into 'the table of excluded studies'.

2.6 Lost to follow up <20%

Equation	YES X	NO

2.6.1 Reasons for loss to follow up

Attrition rate included: Loss to follow up and failure to complete HIV tests

2.6.2 Other reasons for exclusion

3. Methodology

3.1 Study design

RCT	X

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Quasi-experimental	
Cohort	

3.2 Study duration

Month & Year	August 2006

3.3 Eligibility criteria

Participants: HIV exposed infants whose mothers who are HIV-1 positive
Interventions: Exclusive breastfeeding under an antiretroviral
Comparisons: Exclusive formula feeding
Outcomes: HIV infection, Infant mortality, HIV free survival

3.4 Cochrane Collaboration 'Risk of Bias' Tool: Methodological quality/ Risk of bias assessment. Each question or domain should be answered with either; 'LOW RISK' or 'HIGH RISK' or 'UNCLEAR'.

DOMAIN/QUESTION	JUDGEMENT	DESCRIPTION
Sequence generation?	Low risk	Randomisation
Allocation concealment?	Low risk	Centralised controlled trial
Blinding of participants, personnel and outcome assessor?	Low risk and unclear for outcome assessors	Blinding was done from 34 weeks until delivery, after that it was impossible to blind participants. It is unclear whether outcome assessors were blinded or not.
Incomplete outcome data adequately addressed?	Low risk	Intention to treat analysis was done
Study free of selective outcome reporting?	Low risk	No evidence of reporting of desirable results only.
Free of other bias?	Low risk	-

3.5 Participants

Sample size	1200 mothers who gave birth to 1179 infants who could be in the study initially.
Total number included in the analysis	1179
Age during initiation of intervention	From birth
Sex	Male and female
Diagnostic criteria for HIV	Polymerase chain reaction and Enzyme Linked Immuno-sorbent Assay.
Setting	1 city, 1 town and 2 large villages.
Socio-demographic	Low socio economic status

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Country	Botswana
Date of study	27 March 2001- 29 October 2003

3.6 Interventions

Experimental group with or without antiretroviral	
Type	**Duration**
EBF	6 months
Control group with or without antiretroviral	
Type	**Duration**
EFF	6 months

3.7 Outcome measures as stated in the review

(Mark appropriate box)

1. HIV infection	YES X	NO
2. Infant mortality	YES X	NO
3. HIV free survival	YES X	NO

3.8 Outcomes definitions

1. HIV infection: Infants with PCR retested on separate sample or by ELISA at 18 months. Time of infection based on the date of the earliest positive result test.
2. Infant mortality: Death
3. HIV free survival: Death or infection by HIV

4. Results

Number of Patients:		
	Randomised or allocation	**Analysed**
Experimental	588	588
Control	591	591
Total	1179	1179

4.1 Summary data for each intervention group

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Measured at 7 months

1. HIV infection	Event	No event	Total
Experimental group	51	537	588
Control group	32	559	591

Measured at 18 months

1. HIV infection	Event	No event	Total
Experimental group	53	535	588
Control group	33	558	591

Measured at 7 months

2. Infant mortality	Event	No event	Total
Experimental group	28	560	588
Control group	54	537	591

Measured at 18 months

2. Infant mortality	Event	No event	Total
Experimental group	48	540	588
Control group	62	529	591

Measured at 7 months

3. HIV free survival	Event	No event	Total
Experimental group	74	514	588
Control group	73	518	591

Measured at 18 months

3. HIV free survival	Event	No event	Total
Experimental group	86	502	588
Control group	80	511	591

4.2 Continuous data

Outcome	Experimental group (mean±SD)	Control group (mean±SD)	WMD	CI 95%	P- value

4.3 Estimate of effect with confidence interval/ P-value

1. HIV infection	RR	CI 95%	P-value
Experimental group			
Control group			

1. Infant mortality	RR	CI 95%	P-value
Experimental group			
Control group			

1. HIV free survival	RR	CI 95%	P-value
Experimental group			
Control group			

4.4 Subgroup analysis

Outcomes were measured at different age months; 7 and 18 months.

4.5 Miscellaneous

Key conclusions	Breastfeeding with zidovudine prophylaxis was not as effective as formula feeding in preventing postnatal HIV transmission, but was associated with a lower mortality at 7 months. Both strategies had comparable HIV free survival at 18 months.
Other significant comments from authors	The results demonstrate the risk of formula feeding to infants in Sub Saharan Africa, and

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	the need for studies of alternative strategies.
References to other relevant trials	YES
More information required	-
Others:	-

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Data extraction form; Peltier, 2009.

1. Source

Study ID	03
Reviewer	Angel Phuti and Oswell Khondowe
Author & year	Peltier, C. A., Ndayisaba, G. F., Lepage, P., Van Griensven, J., Leroy, V., Pharm, C. O., Ndimubanzi, P. C., Courteille, O. & Arendt, V. 2009
Journal	. AIDS, 23**,** 2415-23.
Title	Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. AIDS, 23**,** 2415-23.
Country	Rwanda

2. Eligibility criteria

(Indicate with a cross the appropriate one)

2.1 Types of studies

Randomised Controlled Trial	
Quasi-experimental	
Cohort study	X
Published data	X
Unclear/NO	

2.2 Types of participants

HIV exposed babies born from HIV-1 positive mothers.	X
Unclear/NO	

2.3 Types of interventions

Exclusive Breastfeeding vs. Formula feeding under a certain antiretroviral or not.	X
Exclusive breastfeeding vs. Mixed feeding under a certain antiretroviral or not.	
Unclear/NO.	

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2.4 Types of outcomes

HIV infection	X
Infant mortality	X
HIV free survival	X
Unclear/NO	

If any of the above answers are 'NO', do not proceed. If study is to be included in 'Excluded studies' of the review, record the information into 'the table of excluded studies'.

2.6 Lost to follow up <20%

Equation	YES X	NO

2.6.1 Reasons for loss to follow up

Reasons for attrition rate included: death and loss to follow up.

2.6.2 Other reasons for exclusion

3. Methodology

3.1 Study design

RCT	
Quasi-experimental	
Cohort	X

3.2 Study duration

Month & Year	May 2005-January 2007

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3.3 Eligibility criteria

Participants: HIV exposed infants whose mothers who are HIV-1 positive
Interventions: Exclusive breastfeeding under an antiretroviral
Comparisons: Exclusive formula feeding
Outcomes: HIV infection, Infant mortality, HIV free survival

3.4 Cochrane Collaboration 'Risk of Bias' Tool: Methodological quality/ Risk of bias assessment. Each question or domain should be answered with either; 'LOW RISK' or 'HIGH RISK' or 'UNCLEAR'.

DOMAIN/QUESTION	JUDGEMENT	DESCRIPTION
Sequence generation?	High risk	Non randomised cohort study
Allocation concealment?	High risk	-
Blinding of participants, personnel and outcome assessor?	High risk	No blinding done
Incomplete outcome data adequately addressed?	Low risk	Intention to treat analysis was done
Study free of selective outcome reporting?	Low risk	No evidence of reporting of desirable results only.
Free of other bias?	Low risk	-

3.5 Participants

Sample size	532
Total number included in the analysis	532
Age during initiation of intervention	From birth
Sex	Male and female
Diagnostic criteria for HIV	HIV DNA PCR test
Setting	Government run facilities: 1 rural, 2 semi rural and 2 urban.
Socio-demographic	Low socio economic status-
Country	Rwanda
Date of study	May 2005- January 2007

3.6 Interventions

Experimental group with or without antiretroviral	
Type	**Duration**

EBF	6 months
Control group with or without antiretroviral	
Type	**Duration**
EFF	6 months

3.7 Outcome measures as stated in the review

(Mark appropriate box)

1. HIV infection	YES X	NO
2. Infant mortality	YES X	NO
3. HIV free survival	YES X	NO

3.8 Outcomes definitions

1. **HIV infection:** positive result test of HIV DNA PCR tested at 6,weeks, 3 months, 7 and 9 months of age.
2. **Infant mortality:**
3. **HIV free survival:** Death or infection by HIV

4. Results

Number of Patients:		
	Randomised or allocation	**Analysed**
Experimental	227	227
Control	305	305
Total	532	532

4.1 Summary data for each intervention group

Measured at 9 months

1. HIV infection	**Event**	**No event**	**Total**
Experimental group	1	226	227
Control group	0	305	305

Measured at 9 months

2. Infant mortality	**Event**	**No event**	**Total**
Experimental group	7	220	227
Control group	17	228	308

Measured at 9 months

3. HIV free survival	**Event**	**No event**	**Total**
Experimental group	11	216	227
Control group	18	287	305

4.2 Continuous data

Outcome	Experimental group (mean±SD)	Control group (mean±SD)	WMD	CI 95%	P- value

4.3 Estimate of effect with confidence interval/ P-value

1. HIV infection	RR	CI 95%	P-value
Experimental group			
Control group			

1. Infant mortality	RR	CI 95%	P-value
Experimental group			
Control group			

1. HIV free survival	RR	CI 95%	P-value
Experimental group			
Control group			

4.4 Subgroup analysis

Outcomes measured at different intervals.

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4.5 Miscellaneous

Key conclusions	Maternal HAART while breastfeeding could be a promising alternative strategy in resource- limited countries.
Other significant comments from authors	
References to other relevant trials	YES
More information required	-
Others:	-

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ANNEXURE II. – Ethical approval

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot • your knowledge partner

13 December 2010 **MAILED**

Ms A Phuti
Department of Nursing
2nd Floor
Teaching Block

Dear Ms Phuti

Exclusive breastfeeding in the prevention of HIV-1 transmission from mother to child – A systematic review.

ETHICS REFERENCE NO: N10/11/391

RE : ETHICAL REVIEW NOT REQUIRED

Thank you for your application. The application is for a systematic review using only data that is available in the public domain therefore the cluster head for Research Ethics has considered this proposal to be exempt from ethical review.

This letter confirms that this project is now registered and you can proceed with the work.

Yours faithfully

MS CARLI SAGER
RESEARCH DEVELOPMENT AND SUPPORT
Tel: +27 21 938 9140 / E-mail: carlis@sun.ac.za
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ANNEXURE III.-prisma 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	I
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Iii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	10,39
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6 28-31
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7, 28-29
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	29-30
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	30-31
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8 Appendix 1:72-89
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, 30-31
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8, 51-53
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	35

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	45-46

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	32-36
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	36-38
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	42
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	44,46,48
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	45,47,49, 51-53
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	45,46,48, 54-57
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	54-58
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	45,47,49, 51-53
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	54-57
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	59-60
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	61-63
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	64
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No funding

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ANNEXURE IV - Editor’s declaration

(See next page, declaration could not fit due to technical issues).