ROLE OF EVIDENCE IN THE DEVELOPMENT OF TREATMENT RECOMMENDATIONS: Application of the grade criteria

by

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M.B.B.S University of Ilorin, 2004

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ABSTRACT

Over the last several decades, the role of clinical medicine in the development of practice guidelines has increasingly become dependent upon evidence. This study aims to examine the role evidence played in the development of the treatment guidelines concerning infant feeding options for babies born to HIV-infected mothers in Sub-Saharan Africa. Clinical outcome data was reviewed from the evidence available from the World Health Organization. Outcomes of interest were assessed based upon the infants either being exclusively breastfed or exclusively formula fed with the relative risks of these outcomes given the exposure calculated and the evidence graded for its strengths and deficiencies within the framework of GRADE. The findings suggest that the evidence had some methodological flaws as well as inconsistencies that resulted in low quality grading. The clinical community would benefit from further research that will likely have an important influence on the confidence of the study estimates.

**Keywords:** Practice Guidelines, Relative Risks, Sub-Saharan Africa; Exclusive breastfeeding, Exclusive Formula feeding, HIV
DEDICATION

To all the children infected with HIV.
ACKNOWLEDGEMENTS

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Finally, my gratitude to the anchor of my faith who was, who is and is to come. Jesus.
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# GLOSSARY

<table>
<thead>
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AFASS</td>
<td>Acceptable Feasible Affordable Sustainable and Safe.</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>EBF</td>
<td>Exclusive Breastfeeding</td>
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<tr>
<td>EFF</td>
<td>Exclusive Formula Feeding</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>MTCT</td>
<td>Mother-to-child transmission</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SSA</td>
<td>Sub-Saharan Africa</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>United Nations Joint Programme on HIV/AIDS</td>
</tr>
<tr>
<td>UNFPA</td>
<td>United Nations Population Fund</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children's Fund</td>
</tr>
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<td>WHO</td>
<td>World Health Organization</td>
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1. INTRODUCTION

1.1 Introduction to the Public Health Question

In 2007, the global prevalence of Human Immunodeficiency Virus (HIV) was reported by the Joint United Nations program on HIV/AIDS (UNAIDS) as less than 1%. By comparison the prevalence of HIV in sub-Saharan Africa was estimated at about 6%, and 4% on the Indian sub-continent (Nduati, 2000, UNAIDS, 2008). On the African continent, available data shows that the prevalence of HIV-1 among pregnant women ranged from 5-10% in West Africa, 10-30% in East and Central Africa and greater than 20% in Southern Africa (Nduati, 2000). These figures show that Africa and, specifically, sub-Saharan Africa, has an importantly higher burden of HIV relative to its population.

Infants born to HIV positive mothers are at risk of being infected at different stages – in utero, intra partum and post partum – chiefly through breastfeeding (Miotti et al, 1998, UNAIDS, 2000). Among non-breastfed infants, most mother to child transfer (MTCT) of HIV is known to take place during the intra partum period, while in breastfeeding populations, 30-50% of the overall transmission is attributable to breastfeeding, making breastfeeding the most significant source of HIV infection in young children (De Cock et al., 2000). Table 1 shows the estimated risks and timing of HIV infection in infants born to HIV-positive mothers.
Table 1 Estimated risk and timing of mother-to-child transmission of HIV in the absence of interventions

<table>
<thead>
<tr>
<th>Timing</th>
<th>Transmission rate (%)</th>
</tr>
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<tbody>
<tr>
<td>During pregnancy</td>
<td>5–10</td>
</tr>
<tr>
<td>During labour and delivery</td>
<td>10–15</td>
</tr>
<tr>
<td>During breastfeeding</td>
<td>5–20</td>
</tr>
<tr>
<td>Overall without breastfeeding</td>
<td>15–25</td>
</tr>
<tr>
<td>Overall with breastfeeding to 6 months</td>
<td>20–35</td>
</tr>
<tr>
<td>Overall with breastfeeding to 18–24 months</td>
<td>30–45</td>
</tr>
</tbody>
</table>


1.2 Purpose of this paper

The purpose of this study is to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence and the strength of the recommendation in respect of infant feeding options for babies born to HIV infected mothers in sub-Saharan Africa.

Practice guidelines for infant feeding options in the developed world have remained unchanged over the past two decades. However, practice guidelines for the developing world and specifically sub-Saharan Africa have undergone a series of revisions, with the most recent joint WHO/UNICEF/UNAIDS/UNFPA policy of exclusive breastfeeding (EBF) recommending EBF for a period of six months (Fletcher et al, 2008, World Health Organization, 2006).

This paper seeks to elucidate the associated risks and benefits of infant feeding options, taking into consideration the factors associated with the transmission of HIV through breastfeeding. The properties of a good practice guideline will be identified through use of the GRADE criteria. GRADE will be applied to the available evidence obtained from the World Health Organization (WHO) and other sources to assess the
quality of the evidence as well as the strength of the recommendation. The impact of this exercise on clinical practice will be assessed, as will the public health implications. Other factors that affect the process of making practice recommendations will also be examined.

1.3 Literature review

The development of antiretroviral (ARV) agents has had an important impact on HIV/AIDS globally, reducing morbidity as well as mortality due to HIV/AIDS. The drugs have also served to reduce the risk of transmission of the disease through prevention of mother-to-child transmission (Fletcher et al, 2008, Mbori-Ngacha et al, 2001).

HIV prevalence and infant mortality rates are lower in the developed world. Practice guidelines have been an aggressive anti-retroviral treatment for the mother to reduce the risk of mother-to-child transmission of HIV, followed by exclusive formula-feeding for the infant. This has been found to reduce the risk of HIV-transmission to the infant to less than 2% (Coovadiaa, H. M. & Kindrab G. 2008). However in resource limited settings, the recommended guideline has varied over the past two decades, ranging from exclusive formula-feeding, an informed choice between formula feeding, breastfeeding, and exclusive breastfeeding (EBF), and most recently, the joint WHO/UNICEF/UNAIDS/UNFPA policy of EBF for a period of six months (Fletcher et al, 2008, World Health Organization, 2006).

In developing countries, feeding infants of HIV-positive mothers has generated much controversy because it involves a choice between two unsatisfactory options. The increased risk of transmission of HIV to the infant in the face of continued breastfeeding must be weighed against an increased risk of infant mortality (despite the reduced risk
of HIV transmission) in the formula-feeding option (Fletcher et al., 2008, Mbori-Ngacha et al., 2001). In the face of high levels of poverty, poor infrastructure, and a lack of clean water, recommendations of replacement feeding\(^1\) option have been postulated to be a counterproductive measure.

The resulting dilemma in developing a guideline for this region involves a trade-off between possible HIV infection and early infant mortality. The joint WHO/UNICEF/UNAIDS consensus statement recommends exclusive breastfeeding (EBF\(^2\)) of infants born to HIV-positive mothers for the first six months of life unless replacement feeding is acceptable, feasible, affordable and safe (AFASS) for mothers and their infants before that time, after which the infants are abruptly weaned (WHO, 2006). The evidence that led to the development of this practice guideline was derived from a number of studies conducted in various countries in sub-Saharan Africa dating back to the late 1990's. The countries include Kenya, Uganda, South Africa, Cote d'Ivoire, Zimbabwe and Mozambique, which counted some of the highest levels of HIV prevalence on the continent. Study methodology varied significantly among countries, from observational studies\(^3\) to randomized trials. WHO feeding guidelines are based on findings from these mixed methods.

\(^1\) Replacement feeding refers to the use of non-breast milk as a means of provision of nutritional support for infants. It ranges from heat-treated breast milk to the use of formula feeds, referred to as replacement feeding in this report.

\(^2\) Exclusive breastfeeding means breastfeeding while giving no other food or drink, not even water, except drops or prescribed medication and mineral or vitamin supplements.

\(^3\) Observational studies include cohort studies, case-control studies, case studies and case series.
2. INFANT FEEDING OPTIONS AND THE GRADE SYSTEM

2.1 Infant feeding options

It is widely accepted that breast milk remains the best feeding option for newborn infants. Breastfeeding has been documented to possess psychological benefits by promoting infant-maternal bonding, while also providing adequate nutritive support for the newborn infant. Breastfeeding has also been reported to offer protective functions, protecting from mortality and morbidity associated with diarrheal diseases, respiratory tract infections, and other infections. Breastfeeding has also been shown to provide some contraceptive functions when practiced exclusively, contributing to improved maternal health and child survival (Sharma & Willingham 1997).

Alternative feeding options have had to be considered in infants born to HIV-positive mothers due to the risk of MTCT. Other options include replacement feeding, encompassing commercial infant formula, home-prepared infant formula, some animal milk, and powdered full cream milk. Alternative feeding options include the use of a HIV-negative wet nurse, heat-treatment of breast milk from HIV-positive mothers, uncontaminated donor milk and, more recently, a short course of EBF with abrupt cessation (Fletcher et al, 2008, Koletzko, 2000). See Appendix 1.

Logistic and practical difficulties have made the other feeding options less attractive and less studied, leaving patients and practitioners with the option of using either EBF or replacement feeding using artificial formula feeds. While the risk of HIV transmission remains in the presence of continued breastfeeding, formula feeding in
resource-poor sub-Saharan Africa carries with it an increased risk of morbidity, adverse outcomes, and mortality. A number of factors have been associated with transmission of HIV through breastfeeding. See Table 2.

### Table 2  Factors associated with transmission of HIV through breastfeeding

**Infant factors**
- Factors associated with the immune system
- Pattern of infant feeding (exclusive breastfeeding versus mixed)
- Morbidity leading to less vigorous suckling, milk stasis and increased leakage of virus across milk ducts (oral thrush)

**Maternal factors**
- Younger maternal age, lower parity
- Maternal seroconversion during lactation
- Clinical and/or immunological (CD4 cell count) disease progression
- RNA viral load in plasma
- RNA viral load in breast milk
- Local immune factors in breast milk
- Breast health (subclinical or clinical mastitis, abscess, cracked nipples) (indirect factor)
- Maternal nutritional status
- Duration of breastfeeding

Source: Adapted from John-Stewart et al. (2004).
2.2 What makes a good recommendation?

Clinical practice involves choices between evidence, values, and scenarios. A treatment decision is made ultimately after weighing the benefits and the drawbacks of the available alternatives. Considerations may include the following:

Consideration of all relevant patient groups:

- Low risk and high risk
- Degree of susceptibility to adverse effects

Consideration of all relevant management options in the case of infant feeding options for infants born to HIV-infected mothers (see Appendix 1):

- Breastfeeding option
- Formula feeding option
- Other available options

Consideration of all patient important outcomes

- Morbidity and mortality profiles
- Quality of life
- Potential toxicity and adverse effects
- Inconvenience cost
- Psychological burden
- Cost to the patient and society

Source: Adapted from Guyatt G. H et al (2008).

Those who develop guidelines have different ways of rating the quality of the evidence and grading the strength of their recommendations. The lack of
standardization has led to end-users finding it difficult to understand the intended messages (Guyatt et al, 2008). The GRADE⁴ system was developed to rectify some of these identified concerns. The GRADE system has been found to provide a comparative advantage when compared to other systems, as shown in the table 3 below:

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Advantages of GRADE over other systems</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Developed by a widely representative group of international guideline developers</td>
</tr>
<tr>
<td></td>
<td>Explicit evaluation of the importance of outcomes of alternative management strategies</td>
</tr>
<tr>
<td></td>
<td>Explicit, comprehensive criteria for downgrading and upgrading quality of evidence ratings</td>
</tr>
<tr>
<td></td>
<td>Transparent process of moving from evidence to recommendations</td>
</tr>
<tr>
<td></td>
<td>Explicit acknowledgment of values and preferences</td>
</tr>
<tr>
<td></td>
<td>Clear, pragmatic interpretation of strong versus weak recommendations for clinicians, patients, and policy makers</td>
</tr>
<tr>
<td></td>
<td>Useful for systematic reviews and health technology assessments, as well as guidelines</td>
</tr>
</tbody>
</table>


The GRADE system categorizes the quality of evidence along a continuum ranging from high to very low. Evidence provided from randomized trials is categorized as beginning from a level of high quality that may be downgraded if a particular number of factors are present. These include: identified study limitations; inconsistencies in the results; indirectness of evidence from clinical trials; imprecision in the reported data; and any identified reporting bias. Observational studies, by contrast, are rated initially as low quality but may be upgraded if the magnitude of the effect is very large or when there is evidence of a dose-response relation (Guyatt et al, 2008).

⁴ Grading of Recommendations Assessment, Development and Evaluation
The GRADE system uses a dichotomous rating system – either strong or weak – based on the strength of a recommendation (Guyatt et al., 2008). Strength is determined by an interplay of factors that include: the balance between the desirable and undesirable effects of the alternatives; quality of the supporting evidence, extent of variability in values and preferences; as well as cost effectiveness. A core principle of the GRADE system is that the both desirable and undesirable outcomes are those that are of importance to the patient, not necessarily the physician or health care provider (Guyatt G.H et al., 2008). It is with the acknowledgement of the role evidence plays in the development of clinical guidelines that led the GRADE working group to conclude that “clinical guidelines are only as good as the evidence and judgments they are based on” (Guyatt et al., 2008).

The need to rate the evidence upon which clinical decisions are based derives from the belief that expert clinicians and organizations in the past, when offering practice recommendations, have not paid sufficient attention to the quality of the evidence (Guyatt GH, Drummond R, eds 2008). Consider, for example, the decade-long prescription of hormone replacement therapy (HRT) for post-menopausal women. Physicians prescribed HRT in the belief that the practice offered protection against adverse cardiovascular events (Stamper & Colditz, 1991). However, the analysis upon which this practice was based was derived from observational studies that produced inconsistent results (Guyatt GH, Drummond R, eds 2008).

A well designed study ultimately refuted these results by showing that HRT may actually have increased the risk of cardiovascular events in post-menopausal women (Hulley et al., 1998, Rossouw JE et al., 2002).
An awareness of the need for high quality research leading to sound evidence prompted us to apply evidence-based criteria to the question of infant feeding for babies born to HIV-positive mothers in sub-Saharan Africa\(^5\). Specifically, we will look at the evidence base supporting the WHO consensus statement that followed the WHO HIV and Infant Feeding Technical Consultation session held in 2006 which on the strength of available evidence made the recommendation within the framework of the GRADE system.

In keeping the principle of GRADE that focuses on patient important outcomes, the focus in this will be on mortality outcomes at a set mid-point of the respective studies as well as at the end-point, the HIV-free survival at both points will also be considered. It is believed that the most important outcome to the patient and caregiver of the three outcomes will be mortality at the end-point of the study and a life that is devoid of HIV and death hence HIV-free survival.

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\(^5\) The geographic region referred to as sub-Saharan Africa (SSA) is the part of Africa that falls below the level of the Sahara desert. It is an expansive part of the continent of Africa, extending from Senegal and The Gambia in the west to Ethiopia in the east and down to South Africa, which represents the southern tip of this geographical entity. The SSA is the region of the world that accounts for the highest HIV disease prevalence as well as some of the highest levels of infant mortality. There are also extremely high levels of poverty in this region.
3. METHODS

3.1 Practice Guidelines

Appendix 1 the shows the various infant feeding options available with a description of risks as well as benefits. As stated earlier, the most recent revision concerning infant feeding policy for babies born to HIV-infected mothers in resource-limited settings recommends exclusive breastfeeding (EBF) for a period of six months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe (AFASS) for mothers and their infants before that time (Fletcher et al, 2008, World Health Organization, 2006).

3.2 Study Population

The study population being considered are the babies born to HIV-infected mothers in Sub-Saharan Africa. The majority of countries in this geographical location are characterized by the World Bank as low-income countries that are conversely resource-limited (World Bank, 2009).

This population is by no means a homogenous one. A wide degree of variation in living conditions exists on the continent as well as within the population of infected mothers, with patients at varying points along the continuum of HIV/AIDS and varying exposures to the disease-altering antiretroviral medication.
3.3 Data Collection and Outcome measures

The evidence used for this analysis was obtained from published randomized controlled trials of feeding options of babies born to HIV positive mothers in sub-Saharan Africa, which compared exclusive breastfeeding with exclusive formula feeding options published by the World Health Organization. The MEDLINE search strategy identified the exact MeSH terms for the following expressions: HIV, Africa South of the Sahara, Breastfeeding and Infant formula. There were additional searches of MEDLINE via PubMed, CINAHL and Cochrane CENTRAL. The searches were supplemented by reports from conference proceedings.

The following outcomes were recorded:

1. HIV transmission at both midpoint and end point of study
2. Mortality at both mid-point and end point of study
3. HIV-free survival at the end of the study.

Observational studies that involved an exclusive formula feeding arm were also considered and compared with other feeding options.

3.3.1 Validity assessment

Methodological information for the assessment of internal validity in keeping with the GRADE criteria was extracted and used to generate evidence profile tables and grade evidence using the GRADEpro 3.2 (The GRADE working team).

3.3.2 Quantitative data synthesis

The results are presented as relative risks and risk differences of being HIV infected, mortality due to postnatal transmission of HIV through breastfeeding, as well
as HIV free survival. Pooled relative risks of the above mentioned outcomes were similarly calculated. To aggregate the data for these outcomes, Review Manager 5 (The Cochrane Collaboration, Oxford, UK) was used with a random effects model. All pooled effect estimates are presented with 95% confidence intervals, with all p values being two-sided.

For each of the pooled studies, we also report $I^2$, the total variation among the studies that is likely explained by inter-study variability rather than chance.
4. RESULTS

4.1 Characteristics of studies

The WHO recommendations for infant feeding options were based on 14 studies, four of which were randomized trials. The remaining ten were observational studies (WHO, 2008). In keeping with the principle of directness of evidence, we excluded two of the randomized trials from the analysis as the comparison was between variations of breast feeding options rather than between breastfeeding and formula feeding. These two studies represent the only studies undertaken in sub-Saharan Africa where the infants were randomized according to feeding modalities. Five of the observational studies were excluded from the analysis because they were abstracts of ongoing trials and the final reports were not located. Results from one study were excluded because they were based on personal communication, not on standard research methods. Four observational studies that involved an exclusive breastfeeding arm were found eligible. It was determined that six studies met the criteria of the research question and were aligned with the GRADE system (See Table 4). These six studies for the analysis of feeding options.

Four outcomes of interest were focussed upon: 1) HIV-infection rates at the midpoint of each study; 2) HIV-infection rates at the end of each study; 3) Mortality outcomes at the midpoint and end of each study; and 4) HIV-free survival data at the end of the study.
Results from the randomized trials were used to assess the effect of the intervention (exclusive formula feeding) in resource-limited sub-Saharan African settings, while results from the observational studies were used to assess the control (exclusive breastfeeding) event rate (baseline risk) of transmission and death in these populations. This method was used because the results from observational studies are known to provide a more representative picture of the event rates in the population. The decision to use the randomized trials to assess the efficacy of the formula feeding intervention is based upon the premise that randomized trials provide the most accurate estimates of treatment effects, especially when methodological approaches are adequate and well reported. In contrast, observational studies tend to be more affected by biases such as lack of randomization and blinding, which introduces some measure of prognostic imbalance. These biases may suggest exaggerated treatment effects (Altman et al, 2001).

4.2 HIV transmission

Two randomized trials (1604 infants) compared EFF to EBF and reported outcomes of HIV transmission at a set midpoint and endpoint of the study. The Mashi study conducted in Malawi had a mid-point of seven months, while the Kenyan study had six months as its mid-point. The end-points of the study were 18 months and 24 months, respectively (Thior et al, 2006, Mbori-Ngacha et al, 2001).

In accordance with the principles of GRADE, the outcome measures were assessed based upon their respective importance. HIV transmission at the end of the study period was deemed the most important outcome for the two studies. The pooled analysis for the overall risk of transmission of HIV at the end of the study period showed
that formula fed infants were more 41% less likely to be infected compared to their breastfed counterparts (RR = 0.59, 95% CI 0.46-0.78) (Appendix 2). The two studies consistently showed that EFF was associated with reduced risk of HIV transmission to an infant. Using the control event rate from the breast feeding group in the trial, the pooled estimates reveal that EFF was associated with between 36 – 84 fewer cases of HIV transmission per 1000 infants. If, however, the pooled control event rate of 19% from the observational studies is used, then formula feeding could result in a reduction of HIV transmission by as much as 78 cases per 1000 infants (CI, 44 - 103). It would require placing 13 infants on formula feeding to prevent one case of HIV transmission.

4.3 Mortality

The pooled analysis of two randomized trials (1604 infants) that compared the mortality profile of the two feeding options (EFF & EBF) (Thior et al, 2006, Mbori-Ngacha et al, 2001) showed a non-significant difference between the two feeding options. Pooled risk difference for mortality at the end of study for the formula feeding option was 1.08 (95% CI 0.83-1.40) (Appendix 3). The absolute effect of formula feeding on mortality was estimated at resulting in as much as 46 more deaths or as low as 20 fewer deaths. No statistically significant heterogeneity was detected with $I^2$ being significant, leading to some concern regarding the inconsistency of the evidence ($p = 0.14, I^2 = 55\%$). With a pooled control event risk of 11% from the observational studies, the use of the formula feeding option could result in a reduction by 19 cases per 1000 infants or 44 more deaths per 1000 cases.
4.4 HIV-free survival

Results from two studies were also pooled for this outcome (Thior et al, 2006, Mbori-Ngacha et al, 2001). The pooled estimates showed a slightly non-significant trend more in favour of the use of exclusive formula feeding (RR = 0.83, 95% CI 0.68-1.01). The point estimates show that formula-fed infants have 17% less risk of dying or contracting HIV at the end of the study period. However, this result is imprecise, as the risk could also mean there is a 1% increased risk. Using the control event rates from the observational study, the use of the formula feeding option would lead to about 75 more cases of HIV free survival (CI; -140, +4). The $I^2$ was moderate and heterogeneity was not statistically significant but inconsistencies do occur in the results ($p = 0.21, I^2 = 37\%$). See Appendix 4.
5. DISCUSSION

5.1 Quality of Evidence using GRADE

Two randomized trials met eligibility criteria in that infants were allocated to exclusive formula feeding (intervention) or exclusive breastfeeding (control). In the application of the GRADE system, a number of factors have been identified that could affect the quality of evidence. The section below deals with the application of these explicit criteria as identified by the GRADE working group (Guyatt GH (2) et al, 2008).

The quality of the evidence from the two studies was downgraded for risk of bias because of several limitations, including the absence of blinding. Blinding of the patients is impossible due to the nature of the interventions, and blinding clinicians may likewise be difficult. Data collectors and analysts should have been blinded. It was also not reported if the laboratory personnel involved with HIV confirmation tests done by DNA PCR (DNA Polymerase Chain Reaction) were blinded as to the arms to which the participants were randomized. Failure to blind data collectors, analysts, and laboratory personnel may have introduced some bias into the outcomes of the studies. There was also some concern with issues of validity, such as allocation of concealment that was not reported. While it is conceivable that allocation of concealment was adequately done but not reported, the likelihood is that allocation was not concealed. Across both study arms the rate of patients lost to follow-up was found to be consistently lower than 10% in the two studies and these rates were lower than the event rates.
There were some concerns with the directness of evidence. Both studies randomized participants to an exclusive breastfeeding arm and exclusive formula feeding arm with similar timeframes; however, the duration of follow-up may be considered inadequate to make sufficient inferences about the effect of breastfeeding on mortality, as well as HIV free survival. The two timelines for the end of the studies were 18 and 24 months for the Mashi and Kenyan studies, respectively. (See Table 4).

The two randomized trials were conducted at two different time periods, with the Kenyan study conducted before antiretroviral agents were available in the country. At the time the Mashi trial was conducted, antiretroviral agents were available as highly active antiretroviral therapy (HAART) for eligible mothers and as prophylaxis for the newborn. The timelines (duration of follow-up) when the outcomes were assessed contributed to some indirectness of the evidence, but it was concluded that the magnitude was not severe enough to warrant a downgrading of the evidence on this account.

The randomized controlled trials were conducted in a variety of settings, including rural and urban settings, to address all population groups that may be resident in the region. Setting choice is pertinent because although a sizable proportion of the African population resides in rural areas, increasing urbanization has meant that there are more people in urban centres, where some of the highest HIV prevalence has been noted. The diversity of the population has also meant that there are participants who may have and may not have been exposed to antiretroviral agents (ARV). Forms of ARV intervention range from single-dose nevirapine at onset of labour to full highly active antiretroviral therapy (HAART), as well as infant prophylaxis.
Concern existed over the precision of the outcome of mortality at the end point of the study \([RR = 1.08 (0.83-1.4)]\) and the outcome of HIV free survival \([RR = 0.83 (0.68-1.01)]\), warranting downgrading of the evidence. The estimates for HIV transmission at the end of the study were, however, precise \([RR = 0.59 (0.46-0.77)]\). See table 7.

The evidence concerning HIV transmission provided consistent results across studies, with no statistically significant heterogeneity \((p = 0.78, I^2 = 0\%)\). The evidence regarding the end-point HIV free survival was not downgraded on account of inconsistencies \((P = 0.21, I^2 = 37\%)\). The evidence for mortality at the end of the study was, however, downgraded for marked inconsistencies as shown in the forest plot in appendix 3 \((P = 0.14, I^2 = 55\%)\). The two studies provided significantly differing estimates concerning risk of mortality across both study arms. Table 7 shows a detailed evidence profile.

The factors that are associated with increased risk of transmission of HIV through breastfeeding are shown in table 2. The lack of adequate infrastructure in some sub-Saharan states, principally lack of safe drinking water, presents an increased risk of mortality to infants who are being formula fed due to the increased risk of diarrhoeal diseases since safe clean water is required for feed preparation. The cost of these preparations in some instances is beyond the means of most mothers and caregivers. The high cost may lead to the onset of mixed-feeding to supplement the formula that is being given. This is borne out of ignorance on the part of the mothers. There is also the issue of cultural correctness and stigma, which may force the mothers to breastfeed the infant to conceal their HIV status (Doherty et al, 2006). Studies have shown, however, that a higher rate of compliance to exclusive formula feeding exists in cases where
there is spousal support with disclosure of HIV status. Spousal support is a factor that should be considered in program planning when the formula feeding option is being considered (Doherty et al., 2006). Since these factors can be assumed present in the context of the randomized controlled trials, this is seen as enhancing the directness of the evidence.

The lack of sufficient studies makes assessing for publication bias through the use of funnel plots impractical. It is, however, assumed that there was no publication bias to warrant a downgrading of the evidence on this account.

5.2 Economic analysis

One of the major concerns in sub-Saharan Africa is the scarcity of resources, leading to a dearth of infrastructure and high levels of poverty, with an attendant weak health care sector that is unable to adequately cater to the needs of the population. Indeed the majority of the response to HIV care and treatment on the continent and more specifically the sub-region is due to donor agencies, multi-governmental organizations and non-governmental organizations. In view of the magnitude of the disease and limited financial resources, a cost efficient option must be adopted to reduce the risk of transmission of HIV to infants while also aiming to reduce the related mortality in the short-term as well as further down the line.

In the literature search for this review, insufficient data existed to address the cost efficiency of either feeding option. However, an attempt was made to do a comparative analysis between the cost that would be incurred if an infant were to be formula fed for a period of six months, then continued on complementary feeds, versus the cost that would arise from the breastfeeding option with attendant transmission of
HIV. These costs will be addressed in two ways: the cost to the patient and caregiver, as well as the cost to the society, which includes the health care sector.

For the breastfeeding option, the cost is minimal as the feeding option is readily available and possesses a number of other benefits as outlined in appendix 1. The option of formula feeding, however, comes at an increased cost to the caregiver and this may be out of the reach for some. It is estimated that infants will consume about 40 tins of 500 grams each in the first 6 months of life. This is the amount of formula estimated to be required to meet the caloric demands of a growing infant. Estimates from a MTCT study in Lusaka estimated the cost of formula feeding an infant for the first year to be about $120 (Maclean & Stringer, 2005). These costs, however, excluded the amounts incurred in procurement of utensils that may be required to prepare the feeds. It also does not account for the cost that may be due to hospital stay for occasional morbidity outcomes. Present estimates in Nigeria are those of a tin of Nestlé’s NAN product costing about ₦800 ($5.8). Over a period of six months this is estimated to amount to about $250 (Verbal conversation with Nigerian HIV physician). In addition, there will be expenses incurred in buying the cup and spoon, as well as buying bottled water in areas where safe drinking water is not readily available. The estimates for these ancillary requirements are presently unavailable.

Breastfed infants have an increased 60% likelihood of contracting HIV from their HIV-positive mothers. According to present estimates, antiretroviral medications in Nigeria cost about $70 on a monthly basis (Verbal conversation with Nigerian HIV physician). In the first year of treatment alone, the cost due to ARV’s is estimated to be about $900. This is without consideration of other medication that may be required on
account of the immune-deficient state and other expenses that may be due to hospital stay.

In both feeding options, there will be cost due to morbidity related to diarrhoeal and respiratory illnesses, which have been reported to be similar in both feeding options. Morbidity due to diarrheal diseases and pneumonia was found to be similar across both study arms in a randomized trial conducted in Kenya (Mbori-Ngacha et al 2001). Observational studies conducted by Magoni et al. reported a significantly higher rate of respiratory tract infections in formula-fed infants but there was no difference in rates of diarrhoeal disease, in keeping with a similar finding reported by the Ditrame Plus study group, which conducted an observational study in Cote d'Ivoire (Becquet et al, 2007).

The high cost associated with HIV positivity among infants and evidence that formula feeding confers upon infants a 41% risk reduction of disease transmission by the second year of life suggests it is cost-effective to formula-feed infants born to HIV-positive mothers. Cost savings from the use of formula feeding could result in a reduction of HIV transmission by as much as 119 cases per 1000 infants, with an assumed control event rate of 22% from the Ditrame study. Similarly, the cost to the health care system and society will be greater in the long term with the breastfeeding option.

5.3 Inconvenience cost

The inconvenience cost due to either feeding option is summarized in Appendix 1.
5.4 Psychological burden

This aspect of the feeding option has not been studied adequately. It is widely reported in the literature that breastfeeding fosters infant-maternal bonding through the establishing and maintenance of eye contact while the baby is suckling on the breast. The impact of the formula feeding option is not well known and will need to be studied more adequately.

There is also the burden of the HIV status of the mother being discovered when it has not been disclosed. The need to hide an individual’s HIV status places significant pressure on the caregiver and may place the infant at risk, as the mother may decide to mix feed with breast milk to assuage the suspicion of neighbours (Doherty T. et al 2006).

5.5 Conclusion

The analysis recommends exclusive formula feeding for babies born to HIV infected mothers in Africa. Results have shown significant effects in reduction of transmission of HIV in the first two years of life. Exclusive formula feeding has also been demonstrated to provide better HIV-free survival at the end of the two-year study period. There was a significant variation in the overall quality of the evidence with HIV transmission at end of study rated as moderate quality, evidence concerning mortality outcome rated as very low quality evidence, and HIV free survival rated as low quality evidence. The findings of this analysis show that desirable effects (HIV free survival, absence of HIV at end point) are closely balanced with undesirable effects. The evidence that supports this conclusion is derived from randomized controlled trials that
are characterized by limitations, such as inconsistent results, imprecision, and methodological flaws.

In view of these the conclusion using the GRADE approach is that the grade of the recommendation is one of weak recommendation provided by low quality evidence (Guyatt GH, Drummond R, eds 2008).

The implication of this conclusion for clinical practice is that further research, if and when performed, is likely to affect the confidence of the estimates and may change these estimates. It’s also possible that alternative strategies to GRADE may be equally reasonable. It is suggested that newer studies be conducted in sub-Saharan African populations of infants born to HIV infected mothers to include all the population groups (ARV-naive and ARV-exposed) with an increased duration of follow-up to enhance external validity. Further, research should also take into consideration the various settings where people live (i.e., rural, urban and semi-urban). Study participants should be randomized into the arms under consideration, with a randomization of adequate culturally relevant patient education given to the caregivers to attempt to confirm the benefits of good patient education as reported by Mbori-Ngacha et al.

It is also suggested that further research be conducted to assess the impact formula feeding has on infant-maternal bonding while also looking at the question of cost-effectiveness of either strategies. Finally, while blinding of subjects may not be possible for ethical reasons, blinding of researchers and data analysts is possible and desirable in order to remove a potential source of bias.
<table>
<thead>
<tr>
<th>Study name/Year</th>
<th>Study arms and participants</th>
<th>Study setting</th>
<th>Follow-up duration</th>
<th>Outcome measures</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thior et al., 2006</td>
<td>Formula feeding plus infant AZT for 1 month: 591 infants vs. Breastfeeding plus infant AZT prophylaxis for 6 months: 588 infants</td>
<td>Urban and rural dwelling</td>
<td>18 months</td>
<td>HIV infection rate at 7 months: RR=0.62(0.41-0.96) 18 months: RR=0.62(0.41-0.94) Mortality rates at 7 months: RR=1.92(1.23-2.99) 18 months: RR=1.29(0.90-1.84) 18 month HIV free survival: RR=0.93(0.70-1.23)</td>
<td>RCT</td>
</tr>
<tr>
<td>Mashi study (2001-2003)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mbori-Ngacha et al., 2001 Kenyan study (1992-1998)</td>
<td>Exclusive formula feeding (EFF): 213 infants vs. Exclusive breastfeeding (EBF): 212 infants</td>
<td>Urban dwelling</td>
<td>24 months</td>
<td>HIV infection rate at 6 months: RR=0.60(0.40-0.89) 24 months: RR=0.57(0.41-0.80) Mortality rates at 6 months: RR=1.29(0.70-2.36) 24 months RR=0.86(0.59-1.27) 24 month HIV free survival: RR=0.72(0.55-0.95)</td>
<td>RCT</td>
</tr>
<tr>
<td>Becquet et al., 2007</td>
<td>Exclusive formula feeding (EFF): 295 infants vs. exclusive short-term breastfeeding (EsBF): (4 months) 262 infants</td>
<td>Urban dwellings</td>
<td>24 months</td>
<td>HIV infection at 24 months: RR=1.04(0.57-1.90) Mortality at 24 months: RR=0.96(0.63-1.47) 24 month HIV free survival: RR=0.92(0.73-1.15)</td>
<td>Open label cohort study</td>
</tr>
<tr>
<td>Ditrame study (2001-2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kagaayi et al., 2008</td>
<td>Exclusive formula feeding: 75 infants vs. exclusive breastfeeding: 107 infants</td>
<td>Rural dwelling</td>
<td>12 months</td>
<td>HIV infection at 6 months: RR=0.23(0.08-0.63) 12 months: RR=0.14(0.05-0.38) Mortality at 6 months: RR=4.76(1.35-16.70) 12 months: RR=6.18(1.83-20.95) 24 month HIV free survival: RR=1.21(0.98-1.48)</td>
<td>Open label cohort study</td>
</tr>
<tr>
<td>ARV-related Maternal-Infant (ARMI) study (2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Infant consumed only formula feeds and no breast milk; infant also was given water, vitamins and prescribed medicines.
7. Infant consumed only breast milk and no other liquids, milk or solid food except vitamins and prescribed medicines.
<table>
<thead>
<tr>
<th>Study name/Year</th>
<th>Study arms and participants</th>
<th>Study setting</th>
<th>Follow-up duration</th>
<th>Outcome measures</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magoni et al, 2005</td>
<td>Formula feeding: 122 infants vs. breastfeeding: 179 infants</td>
<td>Urban dwelling</td>
<td>6 months</td>
<td>HIV infection at 6 weeks: RR=0.25(0.09-0.70)</td>
<td>Cohort study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months: RR=0.29(0.15-0.54)</td>
<td></td>
</tr>
<tr>
<td>Ugandan study (2002)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>South Africa Vertical transmission study (2001 - 2005)</td>
<td></td>
<td></td>
<td></td>
<td>RF: 2/28(7.14%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MBF: 89/332(26.80%)</td>
<td></td>
</tr>
</tbody>
</table>

8 Refers to infant feeding where the source of nourishment does not contain breast milk; usually refers to use of formula feeds.

9 Infant consumed breast milk and either non-human milks such as infant formula or cow milk or solid and semi-solid foods at least once.
<table>
<thead>
<tr>
<th>Study name/Year</th>
<th>Randomization and allocation concealment</th>
<th>Adherence to designated study arm</th>
<th>Blinding</th>
<th>Lost to follow-up</th>
<th>Analysis (Intention to treat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thior et al, 2006</td>
<td>Yes, and probably adequate</td>
<td>Breastfeeding plus infant AZT prophylaxis for 6 months: 57% Formula feeding plus infant AZT for 1 month: 93% (At 4 weeks)</td>
<td>Caregivers - unblind Physician - unblind Data collectors - unblind Data analysts - unblind</td>
<td>Yes Breastfeeding + AZT: 53/588 (9.01%) Formula feeding + AZT: 53/591 (8.97%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Mashi study (2001-2003)</td>
<td>Yes, Using computer generated block randomization, and probably adequate</td>
<td>EBF: 96% EFF: 70%</td>
<td>Caregivers - unblind Physician - unblind Data collectors - unblind Data analysts - unblind</td>
<td>Yes</td>
<td>EBF: 8/212 (3.8%) EFF: 17/213 (7.98%)</td>
</tr>
<tr>
<td>Mbori-Ngacha et al, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6  Methodological quality of observational studies that constitute the WHO evidence base

<table>
<thead>
<tr>
<th>Study name/Year</th>
<th>Study arms</th>
<th>Study design</th>
<th>Intervention/control time frame similar</th>
<th>Intervention/control Setting similar</th>
<th>Effectively blinded assessment of outcome</th>
<th>Lost to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becquet et al, 2007</td>
<td>Exclusive formula feeding (EFF) vs. exclusive short-term breastfeeding (EsBF) (4 months)</td>
<td>Open label cohort study</td>
<td>Very similar</td>
<td>Identical</td>
<td>Not blinded</td>
<td>Yes</td>
</tr>
<tr>
<td>Ditrame study (2001-2005)</td>
<td>EFF: 47/295 infants (16%) EsBF: 58/262 infants (22%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EFF: 47/295 infants (16%) EsBF: 58/262 infants (22%)</td>
</tr>
<tr>
<td>Kagaayi et al, 2008</td>
<td>Exclusive formula feeding vs. exclusive breastfeeding</td>
<td>Open label cohort study</td>
<td>Similar</td>
<td>Identical</td>
<td>Not blinded</td>
<td>Yes</td>
</tr>
<tr>
<td>ARV-related Maternal-Infant (ARMI) study (2005)</td>
<td>EFF: 2/75 infants (2.7%) EsBF: 8/107 infants (7.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EFF: 2/75 infants (2.7%) EsBF: 8/107 infants (7.5%)</td>
</tr>
<tr>
<td>Magoni et al, 2005</td>
<td>Formula feeding vs. breastfeeding</td>
<td>Cohort study</td>
<td>Similar</td>
<td>Identical</td>
<td>Not blinded</td>
<td>FF: 11/122 infants (9.0%) BF: 17/179 infants (9.5%)</td>
</tr>
<tr>
<td>Ugandan study (2002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coovadia et al, 2007</td>
<td>Exclusive breastfeeding (EBF); Replacement feeding (RF) &amp; Mixed breastfeeding (MBF): 35 infants</td>
<td>Open label cohort study</td>
<td>Similar</td>
<td>Identical</td>
<td>Not blinded</td>
<td></td>
</tr>
</tbody>
</table>

10 Refers to infant feeding where the source of nourishment does not contain breast milk; usually refers to use of formula feeds.
11 Infant consumed breast milk and either non-human milks such as infant formula or cow milk or solid and semi-solid foods at least once.
**Table 7  GRADE Evidence profile**

**Question:** Should exclusive formula feeding vs. exclusive breastfeeding be the recommended feeding option?

**Population:** Babies born to HIV infected mothers in sub-Saharan Africa

**Settings:** Urban, semi-urban and rural communities in Africa

<table>
<thead>
<tr>
<th>HIV transmission at end point of study</th>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting bias</th>
<th>Effect</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>Randomized trials</td>
<td>Some limitations 12</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>Not likely</td>
<td>0.59 (0.46 - 0.77)</td>
<td>64 fewer per 1000 (from 36 fewer to 84 fewer)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality at end point of study</th>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting bias</th>
<th>Effect</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>Randomized trials</td>
<td>Some limitations 13</td>
<td>Serious inconsistency 14</td>
<td>No serious indirectness</td>
<td>Serious imprecision</td>
<td>Not likely</td>
<td>1.08 (0.83 - 1.4)</td>
<td>9 more per 1000 (from 20 fewer to 46 more)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End-point HIV free survival</th>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting bias</th>
<th>Effect</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>Randomized trials</td>
<td>Some limitations 15</td>
<td>No serious inconsistency 14</td>
<td>No serious indirectness</td>
<td>Serious imprecision</td>
<td>Not likely</td>
<td>0.83 (0.68 - 1.01)</td>
<td>35 fewer per 1000 (from 66 fewer to 2 more)</td>
</tr>
</tbody>
</table>

12 Neither patients nor physicians were blinded. It was also not explicit if the data analysts were blinded concerning the study arms to which the patients were randomized. The extent to which the concealment of allocation was carried was not stated explicitly. This necessitated a downgrading of the evidence from these studies.

13 Blinding of patients and physicians was not done. Allocation of concealment was also not adequately done.

14 The point estimates for the two randomized trials varied. While one suggested increased mortality with formula feeding, the other was suggestive of increased mortality associated with breastfeeding. The 95% CI for both studies, however, overlapped the threshold of one.

15 Blinding of patients and physicians was not done. Allocation of concealment was also not adequately done.
### Appendix 1

Infant feeding alternatives recommended for HIV-infected mothers in resource-poor settings: benefits and risks

<table>
<thead>
<tr>
<th>Infant feeding alternative</th>
<th>Description</th>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusive breastfeeding (EBF)</td>
<td>Giving the infant no other food or drink not even water apart from breast milk, including expressed breast milk, with the exception of drops or syrups consisting of vitamins, mineral supplements or prescribed medicines</td>
<td>Antibodies protect baby from diarrhea, pneumonia and other infectious diseases. Easily digestible. Child spacing benefits. Cost efficient. Always available. No special preparation needed. Lower risk of transmitting HIV than mixed feeding.</td>
<td>Risk of transmitting HIV to baby. Requires feeding on demand. Mother must be available unless expressed. If expressed, milk must be refrigerated. Mother requires additional calories to support breastfeeding. Solely breastfeeding may raise questions about mother’s HIV status (though less stigma incurred than some other feeding alternatives).</td>
</tr>
<tr>
<td>Mixed feeding (MF)</td>
<td>Breastfeeding a child while giving non human milk such as infant formula or food-based fluid or solid food</td>
<td>Culturally acceptable in most of Sub-Saharan Africa. Cost efficient.</td>
<td>Risk of transmitting HIV to baby, though higher than EBF. Infant more likely to get sick.</td>
</tr>
<tr>
<td>Exclusive Formula feeding (EFF)</td>
<td>Feeding a child infant formula and not breastfeeding at all</td>
<td>No risk of HIV transmission Includes most nutrients needed for infant. Made especially for infant. Others can feed infant.</td>
<td>Costly. Requires clean water. Must be made fresh each time. Infant needs to drink from cup. Infant is more likely to get sick (diarrhea and malnutrition). Not breastfeeding raises questions about mother’s HIV status and may incur stigma.</td>
</tr>
<tr>
<td>Infant feeding alternative</td>
<td>Description</td>
<td>Benefits</td>
<td>Risks</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td>Home-modified animal milk (HMAM)</td>
<td>Feeding a child animal milk and not breastfeeding at all</td>
<td>No risk of HIV transmission. Cheaper than formula. Easily available, especially if family has the animal. Others can feed infant.</td>
<td>Infant more likely to get sick. Must be made fresh each time. Difficult to digest. Multivitamin supplement needed. Must add boiled water and sugar. Mother must stop breastfeeding. Does not contain antibodies. Infant needs to drink from a cup. Not breastfeeding raises questions about mother’s HIV status.</td>
</tr>
<tr>
<td>Heat Treatment of Breast Milk (HTBM)</td>
<td>Expressed breast milk heated at specific temperature to inactivate HIV virus</td>
<td>Antibodies protect baby from diarrhea, pneumonia and other infectious diseases. Easily digestible. Child spacing benefits. Cost efficient. Others can feed infant.</td>
<td>Must be used within 1 h. Infant needs to drink from a cup. Must have boiled water. Mother requires additional calories to support breastfeeding. If not heated correctly, significant loss of antibodies results. Not breastfeeding raises questions about mother’s HIV status.</td>
</tr>
<tr>
<td>Wet nursing (WN)</td>
<td>A woman who breastfeeds baby for another woman</td>
<td>Same nutritional benefits as Breastfeeding. No risk of transmitting HIV to baby if wet nurse is not HIV positive. Cost efficient.</td>
<td>Wet nurse must be confirmed HIV-negative. Wet nurse requires additional calories to support breastfeeding. Wet nurse must protect herself from HIV infection. Inconclusive evidence suggests potential low risk of baby transmitting HIV to wet nurse. Must be available to feed on demand. Wet nursing may raise questions about mother’s HIV status.</td>
</tr>
</tbody>
</table>
## Infant feeding alternatives recommended for HIV-infected mothers in resource-poor settings: benefits and risks

<table>
<thead>
<tr>
<th>Infant feeding alternative</th>
<th>Description</th>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor breast milk (DBM)</td>
<td>Women receive frozen milk donated by HIV negative women in their countries or abroad</td>
<td>Same nutritional benefits as breastfeeding. Cost efficient. Others can feed infant.</td>
<td>Milk must be stored refrigerated or frozen. Lack of continued access to donor milk. Not breastfeeding raises questions about mother's HIV status. Infants must drink from a cup.</td>
</tr>
</tbody>
</table>

Appendix 2

Relative risk of HIV infection with formula feeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya 1998</td>
<td>41</td>
<td>213</td>
<td>71</td>
<td>212</td>
<td>57.3%</td>
<td>0.57 [0.41, 0.80]</td>
</tr>
<tr>
<td>Mashi 2003</td>
<td>33</td>
<td>591</td>
<td>53</td>
<td>588</td>
<td>42.7%</td>
<td>0.62 [0.41, 0.94]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>74</td>
<td>804</td>
<td>800</td>
<td>100.0%</td>
<td></td>
<td>0.59 [0.46, 0.77]</td>
</tr>
</tbody>
</table>

Total events: 144; Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 3.89 (P = 0.0001)

Appendix 3

Relative risk of mortality at the end of the study period with formula feeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya 1998</td>
<td>39</td>
<td>213</td>
<td>45</td>
<td>212</td>
<td>48.4%</td>
<td>0.86 [0.59, 1.27]</td>
</tr>
<tr>
<td>Mashi 2003</td>
<td>62</td>
<td>591</td>
<td>48</td>
<td>588</td>
<td>51.6%</td>
<td>1.29 [0.90, 1.84]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>101</td>
<td>804</td>
<td>800</td>
<td>100.0%</td>
<td></td>
<td>1.08 [0.83, 1.40]</td>
</tr>
</tbody>
</table>

Total events: 181; Heterogeneity: Chi² = 2.22, df = 1 (P = 0.14); I² = 55%
Test for overall effect: Z = 0.58 (P = 0.56)
## Appendix 4

### Relative risk of being dead and/or HIV infected with formula feeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya 1998</td>
<td>58</td>
<td>213</td>
<td>80</td>
<td>212</td>
<td>48.3%</td>
<td>0.72 [0.55, 0.95]</td>
</tr>
<tr>
<td>Mashi 2003</td>
<td>80</td>
<td>591</td>
<td>86</td>
<td>591</td>
<td>51.7%</td>
<td>0.93 [0.70, 1.23]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>138</td>
<td>804</td>
<td>803</td>
<td>100.0%</td>
<td></td>
<td>0.83 [0.68, 1.01]</td>
</tr>
</tbody>
</table>

Total events: 138 for experimental and 166 for control. 
Heterogeneity: Chi² = 1.59, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 1.84 (P = 0.07)
REFERENCES


