

# What are the risks of formula feeding in children of HIV-infected mothers?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: [http://www.who.int/child-adolescent-health/publications/CHILD\\_HEALTH/PB.htm](http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm)

This review addresses the question: *What are the risks of formula feeding in children of HIV-infected mothers?*

The **WHO Pocketbook of Hospital Care for Children** recommends that if the mother is known to be HIV-positive and replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of breastfeeding is recommended. Otherwise, exclusive breastfeeding should be practised if the child is under 6 months of age, and breastfeeding should be discontinued only when these criteria are in place.

These recommendations have recently been updated to include the proviso that the most appropriate infant feeding option for an HIV-infected mother should continue to depend on her individual circumstances, including her health status and the local situation, but should take greater consideration of the health services available and the counselling and support she is likely to receive.

## Introduction:

The human immunodeficiency virus (HIV) pandemic has resulted in a growing number of infants born and living with HIV, with a resultant

impact on child welfare and survival, particularly in the developing world. Whilst the decreasing global price of ARVs has made regimens more accessible to low-income countries, an unresolved problem is the reduction of transmission through breastfeeding.

International child health guidelines have been reluctant to recommend abstinence from breast feeding, due to the known increased morbidity and mortality in HIV-uninfected children who receive replacement feeding [1,2]. Breast feeding is known to protect children of non-HIV infected mothers from infectious disease, including diarrhoea, lower respiratory tract infections and acute otitis media [3,4]. Moreover, breastfeeding is an important part of womanhood, is significant in the development of the mother-child relationship, and avoidance can be associated with social stigma [5].

The development of international guidelines on infant feeding in children of HIV-infected mothers is restricted by the need to provide advice on an individual basis, taking into consideration personal risks and benefits, and regional acceptability of feeding choice.

## Methodology

The Cochrane Database was searched for reviews and randomised trials and a search of the 1966-2007 Medline database of the US National Library of Medicine was conducted using the PubMed clinical search strategy (Infant Formula OR Infant Food) AND HIV AND (HIV Infections/prevention and control OR HIV Infections/transmission) AND (Infant Mortality OR Maternal Mortality OR Morbidity OR Patient Acceptance of Health Care OR Health

Knowledge, Attitudes, Practice). Using the search filters “human” and “English”, 53 articles were sourced, including 11 reviews. All abstracts were read; if there was any doubt as to the relevance of the article, the full text was sourced. Citations listed in relevant trials were also hand searched, yielding a further 6 trials and 3 meta-analyses.

The following studies were included: meta-analyses and analytic epidemiological studies, both observational (case control and cohort studies) and interventional (clinical trials) of HIV-infected women and their children; studies performed in general or specific populations and in hospitals or clinics; studies performed in any country. Papers were excluded if they were non-comparative, if their outcomes related to non-clinical endpoints, if they failed to clearly define comparison groups, if they failed to measure outcomes and exposures in the same objective way, if they failed to identify/control for known confounders and if they were in a language other than English. Methodological quality of included papers was at least type 2b according to the criteria of the Oxford Centre for Evidence-Based Medicine [6].

[http://www.cebm.net/levels\\_of\\_evidence.asp](http://www.cebm.net/levels_of_evidence.asp)

The exclusion criteria applied left a total of 14 papers for review, 5 of which were from the original search strategy and 9 from secondary references.

The primary outcomes assessed were infant death, infant morbidity (as demonstrated by hospitalisation and incidence of infectious disease), and maternal death. Acceptability of feeding choice was also assessed.

## Results

### Feeding modality and maternal mortality:

A randomised clinical trial from Nairobi found a three-fold increased risk of maternal death in the breastfeeding arm (RR, 3.2; 95% CI, 1.3-8.1,  $p=0.01$ ) when compared to women who formula-fed their infants [7]. Using Cox regression models, it was estimated that 69% of the maternal deaths were directly due to breastfeeding.

This observation has not been replicated in further studies. An analysis by Coutsoydis et al of data from 566 women participating in a South

African vitamin A intervention trial found no significant difference between mortality in the breastfeeding and formula feeding cohorts ( $p=0.10$ ) [8]. Equally, a study by Kuhn et al from Zambia found no difference in mortality rates between non-breastfeeders and breastfeeders at 12 months (4.9% vs. 4.9%), or up to 24 months post partum (12.4% vs. 8.39%;  $p=0.38$ ) [9]. Sedgh et al also examined the association between breastfeeding and disease progression in Tanzania, and found the relative risk of death in recent breastfeeders compared to those not breastfeeding was 0.73 (95% CI, 0.29-1.83), controlling for disease stage, CD4 cell count, child survival status and baseline age, education, parity and randomisation arm [10]. A meta-analysis was conducted in 2005 by the Breastfeeding and HIV International Transmission Study Group to appraise this discordance. No significant difference in the risk of mortality between the groups was demonstrated ( $p=0.11$ ), although if breastfeeding was initiated, a lower mortality rate was associated with longer duration of breastfeeding [11].

A more recent study from Nairobi found a higher rate of CD4 cell count decline in current breastfeeders than never-breastfeeders (-7.7 vs. -4.4 cells/ $\mu$ L/month;  $p=0.014$ ) [12]. Moreover, after cessation of breastfeeding, the rate of CD4 cell decline became significantly lower than that of current breastfeeders ( $p=0.003$ ). Using mixed-effect models, BMI decline was also found to be significantly higher in the current breastfeeders (-0.065/month vs. -0.027/month;  $p=0.036$ ) [12]. However, these findings failed to translate into a significant difference in mortality between ever or never breastfeeders (data not shown) [12].

### Feeding modality and infant mortality:

An analysis of seven randomised MTCT trials failed to demonstrate a difference in mortality between ever-breastfed and never-breastfed children, in either HIV-infected or uninfected infants. The adjusted odds ratio for infant death amongst the uninfected children was 0.94 (95% CI, 0.5-1.75,  $p=0.84$ ) in the breast fed compared to never breastfed infants, and 1.08 (95% CI, 0.7-1.68,  $p=0.72$ ) amongst the infected children who breastfed [13]. There was no significant difference in infant mortality through ever breastfeeding when adjusting for infection status (OR, 0.93; 95% CI, 0.65-1.75;  $p=0.70$ ). The major predictor of child mortality was HIV status,

with infection conferring an eightfold risk of death (OR, 8.16; 95% CI, 6.43-10.33) [13].

In contrast, a more recent analysis of two randomised clinical trials in Malawi found that breastfeeding was associated with reductions in mortality of both infected and uninfected infants born to HIV positive mothers [14]. Taha et al found that the risk of death among ever breastfed uninfected infants was 0.34(95% CI, 0.18-0.64), which decreased to 0.11(95% CI, 0.04-0.32) in the exclusively breastfed, uninfected group [14]. This decrease in mortality in the breastfeeding arm was also significant in HIV infected children, although mixed feeding (HR, 0.35; 95% CI, 0.18-0.61) was associated with a lower risk of mortality than exclusive breastfeeding (HR, 0.43; 95% CI, 0.2-0.93). The increased risk of infant death through HIV infection remained; mortality was approximately tenfold higher at 12 months in the infected arm ( $p<0.0001$ ) [14].

A randomised controlled trial from Botswana comparing the efficacy of breastfeeding plus zidovudine for 6 months against formula-feeding plus 1 month zidovudine at reducing mother-to-child transmission of HIV also demonstrated an association between formula-feeding and increased infant mortality [15]. Early infant mortality was found to be significantly higher in the formula-feeding arm when compared to the breastfed infants ( $p=0.03$ ), but the difference in infant death decreased with time so that mortality distribution by 18 months was not statistically different between the two groups ( $p=0.21$ ) [15].

#### Feeding modality and infant morbidity:

A secondary analysis of the randomised trial in Nairobi found an almost identical incidence of diarrhoea (defined by an episode of diarrhoea since the last visit) between infants randomised to receive formula and to breastfeed (HR, 0.9; 95% CI, 0.7-1.1) during the 2 years of follow up, and this difference remained insignificant after stratifying for HIV status. However, an increased incidence of dehydration (HR, 9.7; 95% CI, 1.3-74.0;  $p=0.03$ ) was found in the formula arm during the first 3 months of life, as was the presence of diarrhoea at the time of the follow up visit (HR, 2.1; 95% CI, 1.2-3.8;  $p=0.01$ ) [16]. There was no overall difference in the incidence of pneumonia between formula and breastfed infants (HR, 0.9; 95% CI, 0.7-1.3;  $p=0.74$ ). There was an increased incidence of pneumonia in the formula-fed arm among infected children, but this

was not significant (HR, 1.2; 95% CI, 0.8-1.9;  $p=0.33$ ). The only result of note was a trend for lower incidence of otitis media (HR, 0.6; 95% CI, 0.4-1.0;  $p=0.06$ ), and higher incidence of conjunctivitis (HR, 1.4; 95% CI, 1.0-2.1;  $p=0.09$ ) in the formula-fed group. When stratifying for HIV-infection, there was a significantly higher incidence of sepsis in the formula-fed group (HR, 13.7; 95% CI, 1.4-130.;  $p=0.02$ ) among HIV-infected infants, and an increased risk of hospitalisation between 9-12 months (HR, 8.7; 95% CI, 1.0-74.7;  $p=0.05$ ) [16].

Coutsoudis et al found a significant association between early postpartum (<2months) illness episodes and never breastfeeding, regardless of HIV status (OR, 1.91; 95% CI, 1.17-3.13;  $p=0.006$ ) [17].

#### Acceptability of feeding choice:

Bland et al examined breastfeeding choices in rural South Africa using a longitudinal study and cross-sectional survey [18]. Although the prevalence of HIV is high in rural South Africa, the women studied were unaware of their HIV status. The longitudinal study found that 10% of infants received EBF for 6 weeks, and 6% at 16 weeks, with 46% of infants receiving non-breast milk fluids or feeds within 48hrs of birth. A significant association was found between the mother's intended feeding practice and the feeding pattern at 6 weeks of age ( $p=0.05$ ), although only 20% of women who intended to breastfeed only for 6 weeks succeeded. At 6 weeks, the only factor associated with EBF in univariate analysis was birth in district hospital, rather than clinics, other facilities or home. Supplements were most commonly given for perceived insufficiency of breast milk. Feeding outcome was not significantly associated with source of feeding advice ( $p=0.26$ ). The cross-sectional survey reported rates of EBF as 47% at 2 weeks, 40% at 6 weeks, and 33% at 12 weeks, although these results are limited by the small number of infants involved.

Becquet et al found a similarly low rate of EBF uptake in the Côte d'Ivoire as part of the Ditrane Plus study [19]. Having initiated breastfeeding, the cumulative probabilities of EBF from birth were 0.18 (95% CI, 0.18-0.22), 0.1 (95% CI, 0.06-0.13) and 0.01 (95% CI, 0-0.02) at 1, 3 and 6 months respectively. Failure of early complete cessation of breastfeeding, as per the WHO guidelines, was associated with living with

partner's family (OR, 1.99; 95% CI, 1.01-3.93;  $p=0.04$ ), and having a maternal CD4 count greater than 500 cells/ $\mu$ l (OR, 2.00; 95% CI, 1.01-3.95;  $p=0.04$ ).

A more recent review of the same population has assessed the probability of success of artificial feeding, which was provided free of charge up to 9 months of age, with an oral dose of cabergoline to inhibit lactation [20]. The probability of success of the formula feeding option was 93.6% at day 2 (95% CI, 90.7-96.3) and 84.2% at 12 months (95% CI, 79.9-88.5) [20]. 15.6% of these women breastfed at least once, 41% of whom did so on day 2 because of social stigma or newborn poor health. A significant prenatal determinant for refusing formula feeding was living with the partner [20], mirroring the finding of Becquet et al regarding failure of complete cessation of breastfeeding [19].

## Conclusions

The paucity and disparity of information on infant feeding practice and maternal or infant mortality makes the risk of formula-feeding difficult to assess. Interpreting studies on the use of infant formula in place of breast milk must be approached with caution. For the purposes of the studies, all participants were advised how to use and reconstitute the formula, and access to clean municipal water was assessed. In certain cases, formula was provided free of charge to participants in the studies. It is therefore difficult to apply these findings to a wider population, where conditions are less than ideal for preparing safe formula. Equally, as has been demonstrated, fear of disclosure of HIV status, and desire to adhere to cultural norms, may discourage mothers from maintaining exclusive formula feeding.

Currently, the low uptake of EBF described in HIV positive women and the limited acceptability of exclusive formula feeding suggests that many women in resource-poor areas are practising mixed feeding, which has been putatively linked to increased MTCT of HIV. It is imperative that in areas where the criteria for artificial feeding is not met, women are given counselling using the most up-to-date information in order to provide them with the resources to make the most appropriate infant feeding choice.

At present, exclusive breastfeeding is recommended for HIV-infected women for the first six months of life unless replacement feeding

is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time. If the criteria are met for replacement feeding, complete avoidance of breastfeeding is recommended. However, at present, advice about infant feeding practices should be provided on an individual basis, considering health status and local acceptability, to ensure the best possible long term mother and child health outcomes. Advice should also take into consideration the health services available, and the counselling and support the mother is likely to receive.

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