A systematic review of HIV-free survival by feeding practices

From birth to 18 months

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1 Background

Globally an estimated 33 million (30 million - 36 million) people were living with human immunodeficiency virus type-1 (HIV) in 2007 [1]. Children less than 15 years old accounted for approximately 2.0 million (1.9 million - 2.3 million) of those living with HIV with an estimated 370 000 (330 000 - 410 000) children < 15 years newly infected in 2007 [1]. Sub-Saharan Africa is at the core of the epidemic, home to 90% of the HIV burden worldwide [1].

Vertical transmission of HIV occurs during pregnancy, the birth process, and through breastfeeding [2-3]. In non-breastfed populations, the combined risk of transmission without any interventions is 15-30% [2]. In breastfed populations, the combined risk of transmission in the absence of interventions, in populations who practice prolonged breastfeeding is 35%. The risk of continued HIV transmission through breastfeeding is directly related to the duration of breastfeeding [4]. In developed countries where a combination of interventions are available, vertical transmission of HIV occurs in 1-2% of infants born to HIV infected women [5-10]. In Africa, where prolonged breastfeeding for 18-24 months is commonplace, HIV transmission through breast milk may contribute a further risk of 10-15% [11-13]

Yet, the benefits of breastfeeding, including provision of immunity against non-HIV related infectious diseases, have to be balanced against the risk of HIV transmission and the morbidity and mortality associated with alternative feeding practices [14-17]. According to the World Health Organization (WHO), formula feeding should only be recommended as an alternative to breastfeeding of HIV-exposed infants when it is affordable, feasible, acceptable, sustainable and safe (AFASS)[18]. The WHO criteria are rarely met in developing countries and mixed feeding i.e. a combination of breastfeeding and replacement feeding is common. Mixed feeding is deleterious to an infant's health and chances of survival combining the risk of HIV transmission through breastfeeding with the increased risk of morbidity associated with formula feeding [19]. Furthermore, infants who receive mixed feeds are more likely to acquire HIV infection than their exclusively breastfed counterparts [14].

Recently published evidence has shown that antiretroviral drugs (ARVs), either lifelong antiretroviral therapy (ART) or antiretroviral drug prophylaxis given either to the breastfeeding mother or the infant can reduce the risk of breastfeeding transmission. Although these interventions have demonstrated reduction in the risk of HIV transmission in clinical studies, their effectiveness have not been evaluated throughout the entire duration of breastfeeding or in programmatic settings. In populations where both mother and the infant are HIV-uninfected, the protective benefit of

breastfeeding with regards to survival reduces after 6-12 months of age. Continued breastfeeding until 24 months of age is justified by the benefits apart from survival [20]. In HIV-infected populations, however, shortening the duration of breastfeeding is justifiable because of the risk of HIV transmission associated with continued breastfeeding. However, the most appropriate time to stop breastfeeding in order to promote HIV-free survival at 18 months is unclear especially now that ARV interventions can reduce postnatal transmission. This systematic review assessed the available evidence to determine whether the protective benefits associated with breastfeeding beyond 6 months of age outweighs the risks of continued breastfeeding with respect to HIV transmission - in the presence or absence of ARV interventions. The review addressed the potential effectiveness of breastfeeding with ARV prophylaxis versus replacement feeding alternatives.

2 Purpose

The objective of the systematic review was to pool and evaluate the data on the effectiveness of different infant feeding practices from birth to 18 months in achieving HIV-free survival of HIV-exposed infants. Also to determine the risk of death due to non HIV-related infectious diseases and malnutrition associated with non-breastfeeding of HIV-exposed infants during the same period.

3 Research Question (to be examined through the systematic review)

The following questions were addressed:

1. In infants born to HIV-infected mothers,

   Who are on lifelong ART, or

   Who are known to have CD4 counts >200, >350 but not on ART, or

   Whose CD4 count is unknown,

   Does exclusive breastfeeding up to 6 months of life, in the absence/presence of a prophylactic ARV intervention, compared to mixed breastfeeding / replacement feeding up to 6 months of life, result in better HIV free survival of the infant at 18 months of age?

2. In infants born to HIV-infected mothers,

   Who are lifelong ART, or

   Who are known to have CD4 counts >200, >350 but not on ART, or

   Whose CD4 count is unknown,

   And who have breastfed for the first 6 months of life, does continued breastfeeding until 12 months of life, in the absence/presence of a prophylactic ARV intervention, compared to replacement feeding between 6 and 12 months of life result in better HIV free survival of the infant at 18 months of age?

3. In infants born to HIV-infected mothers,

   Who are lifelong ART, or

   Who are known to have CD4 counts >200, >350 but not on ART, or

   Whose CD4 count is unknown,

   And who have breastfed for the first 12 months of life, does continued breastfeeding until 18 months of life, in the absence/presence of a prophylactic ARV intervention, compared to replacement feeding between 12 and 18 months of life result in better HIV free survival of the infant at 18 months of age?

4. In infants born to HIV-infected mothers and who have been breastfed for some period in the first months of life, does abrupt cessation of breastfeeding e.g. in 2-3 days compared to cessation of breastfeeding accomplished over a period of weeks/months result in greater serious morbidity and mortality in the infant by 12 or 18 months of age?

3 Methods

3.1 Criteria for considering studies for this review

Types of studies

Randomized clinical trials assessing the risk of mother-to-child transmission (MTCT) of HIV associated with different infant feeding practices between birth and 18 months (birth to ~5 months; ~6-11 months; and ~12-18 months) were included in the analysis. The analysis also included other non-randomized clinical trials and intervention cohorts that provided data on HIV-free survival by different infant feeding practices. Studies performed in any country were included. Studies not published in English were excluded from the analysis. Reports published or conference abstracts presented between January 1998 to October 2009 were eligible for inclusion.

Types of participants

HIV-exposed infants from birth to 18 months

Types of interventions

- Breastfeeding (exclusive, non-exclusive or breastfeeding not categorized) from birth to ~5 months, continued breastfeeding to 12 months or 18 months
- Replacement feeding for any period 0-18 months

No consideration was given to the nature of complimentary feeds given in any period

Types of outcome measures

The following outcomes in HIV-exposed infants were assessed:

<u>Primary outcomes</u>

1. HIV-free survival: infants born to HIV-infected mothers who were alive and uninfected at a given point in time (for this review HIV-free survival was reviewed, when data was available, at 6 months, 12 months, and 18 months).

Secondary outcomes

1. HIV transmission
2. Mortality
3. Morbidity due to non HIV-related infectious diseases

Secondary outcome data were assessed at whatever time points were reported in the manuscripts.

3.2 Search methods for identification of studies

3.2.1 Electronic searches

The following electronic databases were searched:

1. Medline

2. Embase

3. CENTRAL

The authors of the review followed the search strategy as outlined in the Cochrane Reviewers' Handbook [21] (See search strategy and full protocol in Annex b.).

3.2.2 Searching other resources

Abstracts from the following conferences were searched:

1. 5th International Aids Conference 2009

2. 4th South African Aids Conference 2009

3. 16th Conference on Retroviral and Opportunistic Infections 2009

The authors of the review contacted the relevant experts and authors of recent trials on HIV and infant feeding to identify other manuscripts due to be soon published and not therefore available through routine the above databases The search strategy was limited to the English language.

3.3 Data collection and analysis

The authors of the study developed the search strategy following the guidelines outlined in the Cochrane Reviewers' Handbook [21]. Following implementation of the search strategy in the electronic databases and conference abstracts, the authors selected the relevant studies to be included in the analysis. The titles of all appropriate abstracts and titles collected from electronic and hand searches were entered into the Endnote reference software. The titles, abstracts and descriptor terms of all downloaded material from the electronic search and hand searches were scrutinized; irrelevant and duplicate texts and articles were discarded. A set of potentially eligible studies were then selected. Subsequently all abstracts were examined by the authors KKN and TC to determine relevance; full texts of relevant articles were obtained. When KKN and TC were unsure of the relevance of a particular abstract then full texts were acquired for full evaluation. There were no randomized controlled trials specifically addressing the questions posed in this review; observational studies and trials established for a different purpose but that provided information of relevance to this review were included.

Selection of studies

KKN and TC independently applied the inclusion criteria in an unblended standardized manner. Studies were evaluated for relevance according to the protocol namely based on the study design, types of participants, exposure and outcome measures. Disagreements between the authors were resolved by consensus. When further information was required to determine the relevance of the study, authors of the reports were contacted to provide further explanation of the data.

Data extraction and management

The authors of the review, KKN and TC, extracted data using a standardized data extraction form. The following characteristics were extracted from each included study:

- Type of intervention
- Eligibility criteria for enrolment into the study
- Assessment of risk of bias: study design, sequence generation, allocation concealment, blinding, loss to follow-up, incomplete outcome data, other potential bias

- Details regarding the study participants: sample size, population characteristics, country where the study performed, HIV diagnostic testing utilized and ages when testing performed
- Intervention studied: method of feeding, definition of feeding practice, manner in which the outcome was collected, frequency and timing of data collection
- Outcome measures: HIV infection status of the child; overall survival; HIV-free survival birth to ~5 months,~6-11 months, and ~12-18 months; morbidity

Assessment of risk of bias in included studies

Risk of bias was assessed according to the guidelines outlined in the Cochrane Handbook [21]. Studies meeting the inclusion criteria were assessed according to the following:

- Allocation concealment;
- Blinding of intervention;
- Blinding of outcome measurement; and
- Completeness of follow up.

Measures of treatment effect

It was not possible to conduct a meta-analysis for this review due to the heterogeneity of the various studies in terms of study design, exposures and outcomes.

Assessment of heterogeneity

The studies were assessed with regards to the way outcomes were reported. Thereafter, the feasibility of pooling study outcomes was assessed in terms of heterogeneity. Pooling of data was not possible due to the heterogeneity in the various studies in terms of design, methods and outcome assessment.

Unpublished data

The authors of the study endeavored to identify and include reports that had not yet been published but that had been submitted or accepted for publication. Where studies as yet unpublished had data

that was of relevance to this review, the authors reported the data but did not include it in the overall results.

4 Results

4.1 Study selection

Initial screening identified 1323 citations; of these, 68 potentially relevant articles were identified. After reviewing the 68 full text articles, 52 reports (seventeen randomized clinical trials, seventeen observational prospective cohort studies, and 18 secondary articles that reported outcomes relevant to this review) met the inclusion criteria for this review (Figure 1 and 2). Eleven studies (12 articles) reported outcomes according to the feeding modality and were included in the WHO Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles.

Figure 1: Electronic databases and conferences searched

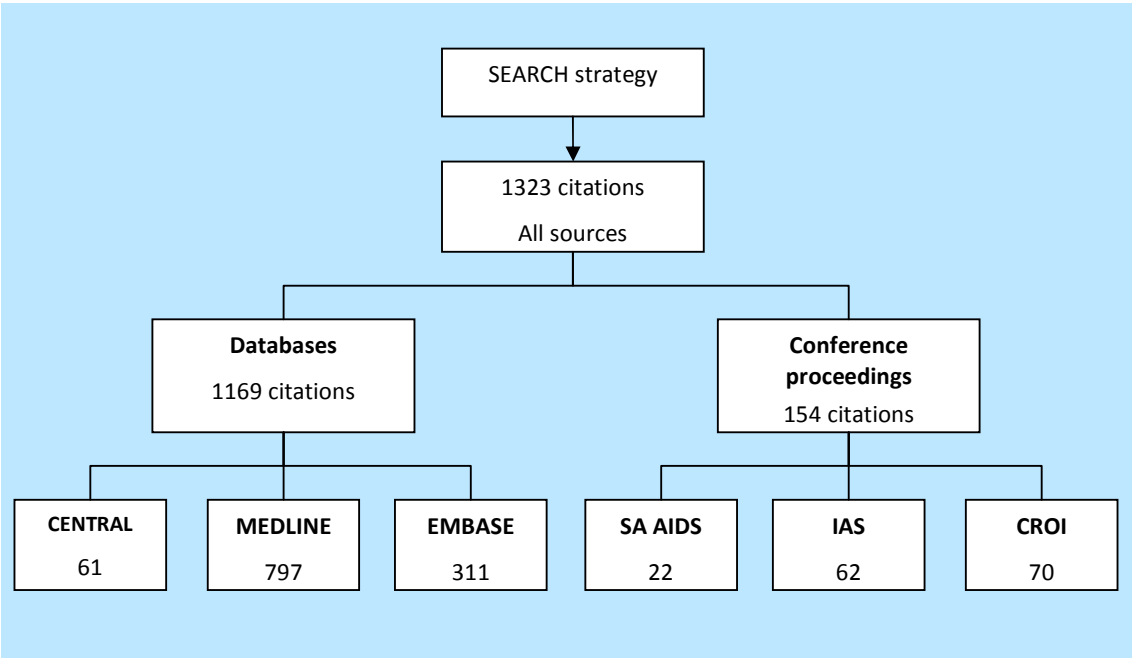
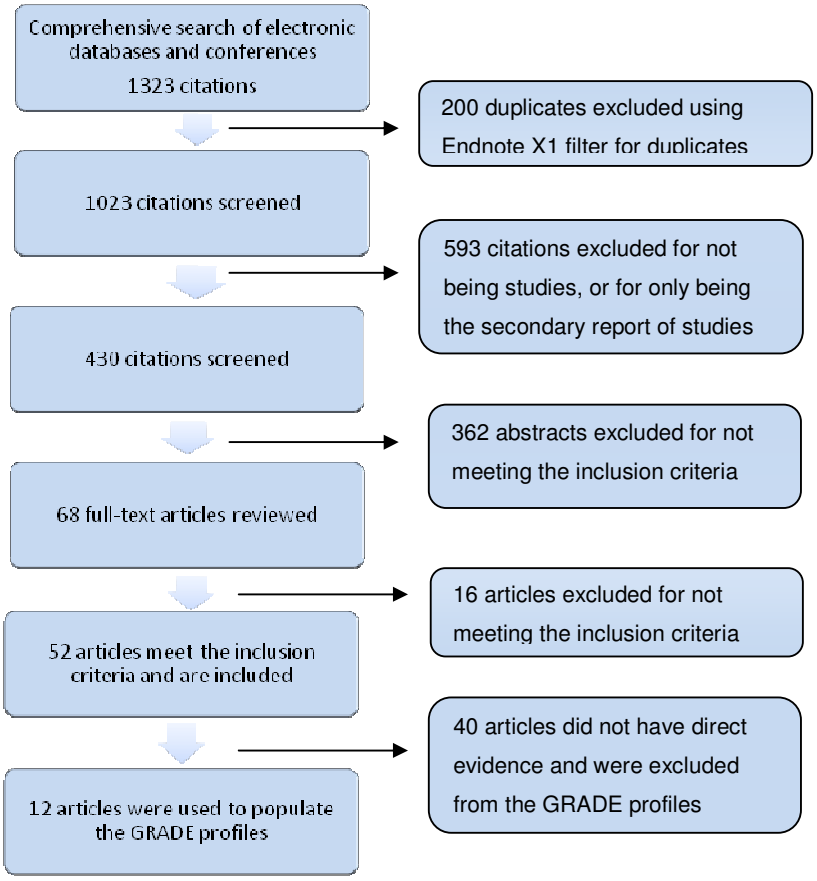


Figure 2: Flowchart of the screening process



4.2 Study characteristics and risk of bias

The characteristics of each individual study and the risk of bias within the studies are included in the Evidence summaries (Annex d).

5 Grade profiles for recommendations

The key outcomes from the review were used to populate the WHO GRADE profiles that were reviewed in the process of revising recommendations [22]. The Grade profiles related to Questions 2 and 3 on continued breastfeeding from 6 to 18 months versus replacement feeding between 6 and 18 months were merged into one grade profile table due to the limited data available for each time period to address these questions. The relative importance of each outcome were then scored 1-9 on the grade profile table: a score of 7-9 indicated that the outcome was of critical importance, an outcome scored as 4-6 was important, and an outcome scored as 1-3 was regarded as not important.

GRADE Profile 1

Question: In infants born to HIV-infected mothers,
who are lifelong ART, or who are known to have CD4 counts >200, >350 but not on ART, or whose CD4 count is unknown
does exclusive breastfeeding up to 6 months of life, in the absence/presence of a prophylactic ARV intervention,
compared to mixed breastfeeding / replacement feeding up to 6 months of life,
result in better HIV free survival of the infant at 18 months of age?

Settings: Botswana, Cote d'Ivoire, Kenya, South Africa, Zimbabwe

Bibliography: Six studies reported primary data with outcomes by feeding modality and were included in the grade profile (see results of Search strategy in report)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	exclusive breastfeeding up to 6 months of life in the absence/presence of a prophylactic ARV intervention	mixed breastfeeding/replacement feeding up to 6 months of life	Relative (95% CI)	Absolute		
HIV free survival of infant 12-24 months											MODERATE	**9**
2 randomised trials	**Mashi [23] 18 months**	serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/483 (84.9%)	80/493 (86.1%)	-5.3 to 2.9%	P=0.60	+++ MODERATE	
	Nduati [24] 24 months	serious[2,3,4,5]	no serious inconsistency	serious	no serious imprecision	none	HIV infections and deaths 80/197 (40.6%)	58/204 (28.4%)			++ LOW	
1 observational study	**VTS [25] 18 months (n=592)**	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient	0.75 (95%CI 0.72-0.78)	Mixed 0.79 (0.70-0.86) Replacement 0.80 (0.72-0.87)			+++ MODERATE	
HIV transmission 12-24 months											MODERATE	**9**
3 randomised trials	**Mashi [23] 18 months**	serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/493 (6.0%)	53/481 (9.5%)	-6.7 to -0.5%	P=0.02	+++ MODERATE	
	Nduati [24] 24 months	serious[2,3,4,5]	no serious inconsistency	serious	no serious imprecision	none	N=142 36.7% (29.4 – 44.0%)	N=128 20.5% (14.0 – 27.0%)		P=0.001	++ LOW	
	ZVITAMBO [15] 18 months	serious[3,6,7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	n=156 6.94% (2.03 – 12.89%)	n=1414 13.92% (11.63 – 16.26%)			+++ MODERATE	
3 observational studies	**VTS [25] 18 months**	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient	9.1 cases per 100 child years		5.8 to 12.5		+++ MODERATE	
	DITRAME	no serious	no serious	no serious	no serious	dose response	2% (0.96-0.99)	1% (0.97-1.00)		P<0.001	+++	

	PLUS [26] 18 months	limitations	inconsistency	indirectness	imprecision	gradient					MODERATE	
	VitA [16] 12 months	serious[7,10]	no serious inconsistency	no serious indirectness	serious[2,3,10]	none	0.221 (0.245 – 0.307)	0.333 (0.253 – 0.415)			++ LOW	
	VitA [16] 15 months						0.247 (0.160 -0.344)	0.359 (0.267 – 0.451)				
Infant Mortality 12- 24 months											MODERATE	**9**
2 randomised trials	**Mashi [23]**	serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62/512 (10.7%)	48/529 (8.5%)	-1.2 to 5.6%	P=0.21	+++ MODERATE	
	Nduati [24] 24 months	serious[2,3,4,5]	no serious inconsistency	serious	no serious imprecision	none	N=114 24.4% (18.2 – 30.7%)	N=121 20.0% (14.4 – 25.6%)		P=0.30	++ LOW	
1 observational study	**VTS [25] 18 months N=592**	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient	Exclusive breastfeeding 0.86 (0.83 – 0.88)	Mixed 0.87 (0.78 – 0.93) Replacement 0.87 (0.78 – 0.92)			+++ MODERATE	

[1] Post-randomization selection bias
[2] Loss to follow up
[3] The study was not blinded
[4] Non-adherence to assigned intervention
[5] Feeding practice not defined
[6] Feeding practice not consistent with WHO guidelines
[7] Feeding history not detailed well - recall bias
[8] Randomization to drug regimen rather than feeding practice
[9] Endpoint not stratified by feeding practice
[10] Reverse causality

GRADE Profile 2.

Note. The Grade profiles related to Questions 2 and 3 on continued breastfeeding from 6 to 18 months versus replacement feeding between 6 and 18 months were merged into one grade profile table (below) due to the limited data available for each time period to address these questions.

Question: In infants born to HIV-infected mothers,
who are on lifelong ART, or who are known to have CD4 counts >200, >350 but not on ART, or whose CD4 count is unknown, and
who have breastfed for the first 6 months of life
does continued breastfeeding from 6 to 18 months of life, in the absence/presence of a prophylactic ARV intervention,
compared to replacement feeding between 6 and 18 months of life
result in better HIV free survival of the infant at 18 months of age?

Settings: Kenya, Tanzania, Zambia, Zimbabwe

Bibliography: Four studies reported primary data with outcomes by feeding modality and were included in the grade profile (see results of Search strategy in report)

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	breastfeeding from 6 to 18 months of life, in the absence/presence of a prophylactic ARV intervention	replacement feeding between 6 and 18 months of life	Relative (95% CI)	Absolute		
HIV free survival of infant 12-24 months											**VERY LOW**	**9**
2 randomised trials	**ZEBS [27] 24 months**	no serious limitations	no serious inconsistency	Serious[11]	no serious imprecision	none	64%	68.4%		P=0.13	++ LOW	
	Nduati [24]	serious[2,3,4,5]	no serious inconsistency	Serious[11]	no serious imprecision	none	59.4%	71.6%			+ VERY LOW	
HIV transmission 12-24 months											**LOW**	9
3 randomised trials	**ZEBS [27]**	no serious limitations	no serious inconsistency	Serious[11]	no serious imprecision	none	LPNT 6.2%	8.8%		P=0.19	++ LOW	
	MICRO [28] 18 months	serious[2,7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/312 (13.3%)		9.1 – 17.5%		++ LOW	
	MICRO [28] 24 months						37/312 (17.9%)		11.2 – 24.5%			
	ZVITAMBO [15] 18 months	serious[3,6,7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	LPNT 8.5%		5.47 – 11.63%		++ LOW	
Infant Mortality 12- 24 months											**VERY LOW**	**9**
1 randomised	**ZEBS [27]**	no serious limitations	no serious inconsistency	Serious[11]	no serious imprecision	none	24.6%	23.9%		P=0.96	+ VERY LOW	

trial												

[1] Post-randomization selection bias
[2] Loss to follow up
[3] The study was not blinded
[4] Non-adherence to assigned intervention
[5] Feeding practice not defined
[6] Feeding practice not consistent with WHO guidelines
[7] Feeding history not detailed well - recall bias
[8] Randomization to drug regimen rather than feeding practice
[9] Endpoint not stratified by feeding practice
[10] Reverse causality
[11] Indirect evidence

GRADE Profile 3.

Question: In infants born to HIV-infected mothers and who have been breastfed for some period in the first months of life, does abrupt cessation of breastfeeding e.g. in 2-3 days compared to cessation of breastfeeding accomplished over a period of weeks/months result in greater serious morbidity and mortality in the infant by 12 or 18 months of age?

Setting Botswana, Malawi, Tanzania, Uganda, Zambia

Bibliography: Six studies reported primary data with outcomes by feeding modality and were included in the grade profile. (see results of Search strategy in report)

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	abrupt cessation of breastfeeding e.g. in 2-3 days	cessation of breastfeeding accomplished over a period of weeks/months	Relative (95% CI)	Absolute	Quality	
Infant Mortality 12-24 months											**MODERATE**	**9**
2 randomised trials	**ZEBS [27]**	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	None	23.9%	24.6%	(P=0.96).		++++ HIGH	
	MASHI [23]	serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	None	63/591 (10.7%)	51/588 (8.7%)			++ LOW	
2 observational studies	**MITRA PLUS [29]**	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/386 (8.5%)	40/350 (9.2%)			++ LOW	
	HOMSY [30]	serious[2,5,8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/23 (56.5%)	2/23 (8.7%)			++ LOW	
Infant Morbidity 12-24 months											**MODERATE**	**8**
3 randomised trials	**ZEBS [27]**	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	None	risk of diarrhoea	Greater in weaned group	2.3 – 4.0	3	++++ HIGH	
	MASHI [23]	serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	None	Hospitalization 20.3%	15.6%	P=0.04		++ LOW	
	PEPI [31-32]	serious[4,5,6]	no serious inconsistency	no serious indirectness	no serious imprecision	None	Frequency of reported gastroenteritis (weaning at 6 months)	7 weeks–3 months: 1.6% (25/1635) 4-6 months: 4.1% (63/1546) 7-9 months: 9.0% (129/1427)			++ LOW	
1 observational studies	**NVAZ [32-33]**	serious[1,7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Frequency of reported gastroenteritis	7 weeks – 3 months: 1.9% (25/1302) 4-6 months: 6.4% (79/1239)			+++ VERY LOW	

								7-9 months: 9.2% (107/1168)				

[1] The study was not blinded
[2] Loss to follow up
[3] Post-randomization selection bias
[4] Endpoint not stratified by feeding practice
[5] Collection of feeding data not detailed
[6] Randomized according to drug regimen not feeding practice
[7] Feeding practice not defined
[8] Confounders not adjusted for - socio-demographics and infant birth weight

6 Discussion

The findings of this review were formulated as GRADE profiles and presented at a meeting to review the World Health Organization recommendations on HIV and infant feeding meeting. The review summarized the evidence of the impact of breastfeeding or replacement feeding of infants born to HIV-infected women in terms of HIV-free survival at 18 months in settings.

The review assessed that the quality of the evidence available on each of the four 'research' questions (section 3) was only of moderate to low quality. This is distinct from the quality of the studies themselves and their implementation but reflects some limitation of the data when applied to these exact questions e.g. indirectness (data was not primarily collected for this purpose), imprecision (small sample size), inconsistency (variance between results of studies) or another study design limitation.

The review found that there was:

i. moderate quality evidence to support exclusive breastfeeding up to 6 months compared to replacement feeding or mixed feeding [15-16, 23-26],

ii. low to very low grade evidence to support continued breastfeeding for 6 to12 months and 12 to 24 months respectively [15, 25, 27-28], and

iii. moderate quality evidence that abrupt cessation of breastfeeding or weaning had adverse health outcomes in terms of morbidity and mortality between 12 to 24 months of life [23, 27, 29-31, 33].

See detailed Grade profiles - Annex d.

Although the quality of evidence supporting the continuation of breastfeeding after 6 months was of low to moderate quality, the significance of this findings should be considered along side the evidence on antiretroviral interventions to reduce postnatal transmission of HIV and also the survival and other benefits of breastfeeding in HIV unexposed infants. These interventions have been shown to reduce postnatal transmission of HIV to the infant either through the use of prophylactic antiretrovirals given antenatally to mothers and continued throughout the duration of breast feeding [29, 34-35], or the use of maternal prophylaxis and extended nevirapine prophylaxis to the infant [31, 36].

The strength of the systematic review lies in the application of an objective methodology to search and capture evidence from reported studies. In this review, the GRADE process was adopted to make "judgments about the quality of the evidence and the strength of recommendations" [22]. The quality of evidence was ascertained based on the study design, quality, consistency and directness in an objective manner. The strength of recommendations were then determined by the Guideline Development Group after being informed by the systematic reviews.

The studies included in the systematic review, although conducted in developing countries, were usually conducted in research settings, may not have been established to address the questions of interest to this review and may not therefore be generalizable to all other settings. The main limitation of the systematic review was that the patient population, study design, intervention studied and the outcome in terms of HIV-free survival were not the same across the studies. Hence, data from the individual studies could not be combined f and a meta-analysis could not be undertaken. Moreover, although several investigators were contacted by the authors, only one study that had been accepted for publication but was not yet in the public domain was included in the review [29]. There were several limitations of the randomized controlled trials included in the review. Blinding of participants to feeding method was not possible. Most studies were primarily designed as drug trials with mode of infant feeding recorded as a secondary exposure. Randomization by feeding modality was therefore not performed. Of the 17 randomized controlled trials included in this review, only two randomized according to feeding duration or method [24, 27].

Methodological issues may have influenced the outcomes reported in observational studies of infant feeding and HIV free survival; poor attrition rates, inconsistency in the definition of feeding variables with WHO guidelines, recall bias with inadequate specification of the pattern and duration of infant feeding, and variable quality of the studies.

In the context HIV the decision on which infant feeding practice provides greatest benefit is complex. The protective benefits of exclusive breastfeeding to child survival have to be balanced against the risk of HIV transmission through breastfeeding and the advantage of avoidance of all HIV transmission risk associated with replacement feeds needs to be balanced with the increased risk of non-HIV related infections and death associated with non-breastfeeding, in particular, diarrhea, pneumonia and malnutrition [14-17]. Moreover, the choice of which feeding modality might be best for any individual mother and her infant is marred by confusion among health care providers and counselors about HIV and the most appropriate infant feeding choice [37-39]. The difficulty of implementing infant feeding guidelines is further complicated by cultural norms and other social expectations. This consequences of these dilemmas were illustrated in South Africa where, despite

intense support and counseling being available to support either exclusive breastfeeding or replacement feeding, inappropriate feeding practices were common with resulting increased mortality [25].

Finally, although there is strong evidence for HIV-infected women to exclusively breastfeed for 6 months, the decision on continued breastfeeding remains unclear and further evidence is required. Very limited data was identified through this review to specifically inform this issue. Although new interventions exist to reduce the postnatal transmission of HIV through breastfeeding and may provide opportunity for more safely continuing to breastfeed after 6 months versus, the studies that are assessing the use of prophylactic antiretroviral therapy throughout the entire duration of breastfeeding are not yet close to reporting their findings.

7 Contributions of authors

T Chetty wrote the protocol, screened citations, selected and reviewed the studies for inclusion in the review and the grade profiles, assessed characteristics and the risk of bias of included studies, revised the grade profiles and wrote the report. KK Naidu contributed to the development of the protocol, screened abstracts, selected and reviewed studies for inclusion in the review, developed and revised the grade profiles, assessed the characteristics and risk of bias of included studies, and edited and reviewed the report. ML Newell contributed to the protocol design, reviewed and assessed characteristics and the risk of bias of included studies, and reviewed and edited the report

8 Declaration of interest

None

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