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Impact of Breastfeeding on Cytomegalovirus Transmission in HIV-Exposed Infants: Systematic Review and Meta-Analysis

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Abstract

Background

In the setting of maternal HIV-1, infant CMV infection is associated with impaired growth and development. HIV-1/CMV co-infected infants have a high risk of mortality, neurologic deficits, and HIV-1 disease progression. Infants may acquire CMV in utero, during delivery, or postnatal through breast milk or saliva. Maternal CMV antibodies protect against congenital disease and infection; but postnatal protection wanes rapidly. In sub-Saharan Africa, 80% of children acquire CMV during the first year of life, and acquisition may occur earlier if mothers have HIV-1. HAART started during the third trimester may decrease infant CMV infections, by mechanisms independent of breast milk CMV levels. Preventing or delaying CMV infection may represent a novel strategy to improve the health of both HIV-infected and HIV-exposed uninfected infants in sub–Saharan Africa, but requires a better understanding of CMV replication and transmission in the setting of maternal HIV-1. This review is focus on those issues and highlights different interactions between cytomegalovirus, HIV, antiretroviral therapy and breastfeeding.

Objectives

To investigate whether breastfeeding increase the risk of cytomegalovirus infection in HIV-exposed infants.

To evaluate whether antiretroviral therapy prophylaxis could decrease cytomegalovirus breastfeeding infection in postpartum.

Search methods

We searched Cochrane Central Register of Controlled Trials (CENTRAL), Scorpus, PubMed,LILACS, Web of Science and Clinicaltrials. Moreover, we performed hand searches in different website conferences, such as the International AIDS Conferences and the annual Conferences on Retroviruses and Opportunistic infections. JT and LM extracted data in the study eligibility form.

Selection criteria

We selected randomized controlled trials (RCTs), non -randomized control trials, quasi-randomized control trials and prospective cohort studies assessing cytomegalovirus transmission in HIV-exposed infants through breastfeeding.

Data collection and analysis

JT and EM independently identified and assessed eligible studies that met inclusion criteria. Study design, characteristics of study populations, interventions, controls and results were extracted by JT and EM. Moreover, the risk of bias was assessed independently by JT and EM. We conducted meta-analysis when the population, the intervention, the outcomes and the study design were as similar as possible. We reported the odds ratio, the risk ratio and the mean difference with their respective 95% confidence intervals for the different outcomes.

Main results

The review has shown that breastfeeding HIV-exposed infants were 77% in risk of developing CMV infection compared to no breastfeeding and/or formula feeding (OR 0.23 95% CI (0.04 to 1.32), 5 studies, 1007 infants, P=0.10), this result was not statistically significant. Antiretroviral therapy was effective in reducing 83% of CMV infection compared to no antiretroviral therapy or antiretroviral prophylaxis (OR 0.17 95% CI 0.03 to 0.94, 3 studies, 560 infants, P= 0.04).

The calculated mean difference of time to CMV infection between breastfeeding HIV-exposed infant group and control was 5.61 months 95% CI [5.34, 5.88]. We can conclude that breastfeeding increase the mean difference of time to CMV infection high as 5.34 months and as low as 5.88 months compared the control group. This result was highly statistically significant with P < 0.00001. In breastfeeding HIV-exposed infants, cytomegalovirus screening was 47% effective in >= 4 months compared to < 4 months of age (RR 1.47 95%CI 1.13 to 1.93, 1 study, 146 infants, P= 0.005). CMV DNA and CMV PCR were statistically significant in breastfeeding HIV-exposed infants, with 63% (OR 0.37 95% CI (0.20 to 0.67), 5 studies, 1823 infants, P=0.001) and 50% (OR 0.50 95% CI 0.30 to 0.84, 2 studies, 365 participants, P=0.009), respectively compared to the control group. Lastly, the review has illustrated that breastfeeding HIV-exposed infants who were positive in CMV PCR were 42% in risk of dying compared to the

compared group (RR 1.42 95% CI 0.57 to 3.57, 3 studies, 1426 infants, P=0.46). The overall evidence was graded very low for CMV infection, CMV DNA and all cause of mortality. However, CMV screening was graded low; time to CMV infection CMV IgG were graded moderate.

Authors' conclusions

This review has shown CMV infection occurs frequently in breastfeeding HIV-exposed infants. This infection is more likely to happen in the last months of exclusive breastfeeding. However, maternal antiretroviral therapy could decrease significantly CMV infection in HIV-exposed children. In addition, this study illustrated that CMV should be screened above four months postnatal because CMV infection is acquired around five months post natal. Then, we urge further research in this field so that CMV infection could be minimized in HIV-exposed infants in the last months of exclusive breastfeeding. Therefore, this review should be taken in a context of several limitations.

Keywords: HIV-exposed uninfected; cytomegalovirus; infants; breastfeeding

Background

Description of the condition

Most African infants acquire CMV infection during infancy (Kaye 2008; Gompels 2012; Filteau 2016). Studies have shown the risk of congenital CMV infection was higher among infants of HIV-infected than uninfected mothers (Mwaanza 2014; Filteau 2016). Increased infections with maternal HIV exposure could result from maternal CMV reactivation, which is common in HIV-infected women with low CD4 counts (Filteau 2016).

In the setting of maternal HIV-1, infant CMV infection is associated with impaired growth and development (Gompels 2012; Roxby 2014) and HIV-1/CMV co-infected infants have a high risk of mortality (Slyker 2009; Roxby 2014), neurologic deficits (Kapetanovic 2012; Roxby 2014), and HIV-1 disease progression (Kovacs 1999; Roxby 2014). Infants may acquire CMV in utero, during delivery, or postnatally through breast milk or saliva (Kaye 2008; Roxby 2014). Maternal CMV antibodies protect against congenital disease and infection; but postnatal protection wanes rapidly (Manicklal 2013; Roxby 2014). In sub-Saharan Africa, 80% of children acquire CMV during the first year of life (Kaye 2008; Roxby 2014), and acquisition may occur earlier if mothers have HIV-1 (Slyker 2009; Roxby 2014).

CMV may be transmitted in utero as a result of primary maternal infection or recurrent infection resulting from reinfection with a new CMV strain or reactivation of latent virus (Ahlfors 1982, Lanzieri 2013) CMV may also be acquired perinatally via exposure to infected maternal genital secretions during delivery, or postnatally by blood transfusion or infected breast milk (Stagno 1980; Lanzieri 2013). CMV sero-prevalence among women in the reproductive age ranges from 45% in

developed countries to 100% in developing countries (Plosa 2012, Anigilaje 2015), showing that CMV infection is a serious public health issue in general in developing countries. A full appreciation of CMV as a pathogen contributing to morbidity and mortality in a variety of immunocompromized hosts is well established (Manicklal 2013).

The low profile of congenital CMV can be explained by the following factors (Manicklal 2013). First, most maternal and newborn infections are asymptomatic and therefore are not recognized at birth (Manicklal 2013). Second, sequelae from congenital CMV infection are frequently delayed in onset, at which point a retrospective diagnosis is challenging (Manicklal 2013). Third, the dogma that congenitally infected children who are born to women with preexisting antibodies have normal outcomes has led to inattention to congenital CMV in developing countries (Manicklal 2013). Emerging data from highly seropositive populations, which are usually in developing countries, however, suggest that not only is the rate of congenital CMV infection higher than in developed countries but it is an important cause of hearing loss in resource-limited settings (Mussi-Pinhata 2009; Yamamoto 2011; Manicklal 2013).

Prior to the advent of highly active antiretroviral therapy (HAART), reported congenital CMV rates were high among HIV-exposed and HIV-infected infants (Doyle 1996, Chandwani 1996, Meyer 2014). However, studies of congenital CMV in the HAART field show lower rates of congenital CMV in HIV-exposed, uninfected infants (Guibert 2009; Meyer 2014). In contrast to congenital CMV transmission, peri- or postpartum CMV transmission is typically asymptomatic in healthy full-term infants. However, peripartum CMV acquisition in HIV-infected infants is an important predictor of morbidity and mortality (Slyker 2009, Meyer 2014), leading to higher rates of HIV-1 progression (Meyer 2014). Mounting evidence suggests that growth and development of HIV-exposed, uninfected infants are also adversely affected by perinatal CMV acquisition (Meyer 2014). This review will investigate all aspect of CMV transmission through breastfeeding in HIV-exposed infants.

Description of the intervention

Despite significant scale-up of antiretroviral prophylaxis, 260,000 pediatric HIV-1 infections are still diagnosed annually (UNAIDS 2013, Meyer 2014) of which nearly half are a result of breastfeeding (Meyer 2014). Therefore, babies who are not breastfed exclusively for the first three to four months are more likely to suffer health problems such as gastroenteritis (Howie 1990; Ip 2007; Kramer 2012; Quigley 2007), respiratory infection (Ip 2007; Kramer 2001;Victora 1989; Wright 1989), otitis media (Aniansson 1994; Duncan 1993; Ip 2007), urinary tract infections (Marild 1990; Pisacane 1992), necrotizing enterocolitis (Ip 2007; Lucas 1990), atopic disease if a family history of atopy is present

(Burr 1989; Lucas 1990a; Saarinen 1995) and diabetes mellitus (Karjalainen 1992;Mayer 1988; Virtanen 2014). Research also indicates a positive relationship between having been breastfed and the bone health of the child (Lucas 1990) and with improved cognitive development (Kramer 2008). Another significant viral pathogen that is vertically transmitted is cytomegalovirus (CMV). HAART started during the third trimester may decrease infant CMV infections, by mechanisms independent of breast milk CMV levels (Slyker 2016). The large French Perinatal Cohort Study has showed lower rates of congenital CMV infection in HIV-exposed-uninfected infants in the cART era (1.2%), compared with the pre-cART era (3.5%), particularly if cART began in the first trimester among HIV-infected infants (Guibert 2009).

How the intervention might work

CMV is found in both whey and cellular fractions of breast milk (Hamprecht 2001) and could have multiple sources, including mammary epithelial cells and migrating monocyte/macrophages and lymphocytes. In the setting of maternal HIV-1 infection, local HIV-1 replication and immunosuppression within tissues could increase CMV shedding at sites relevant for CMV transmission (see figure 1).

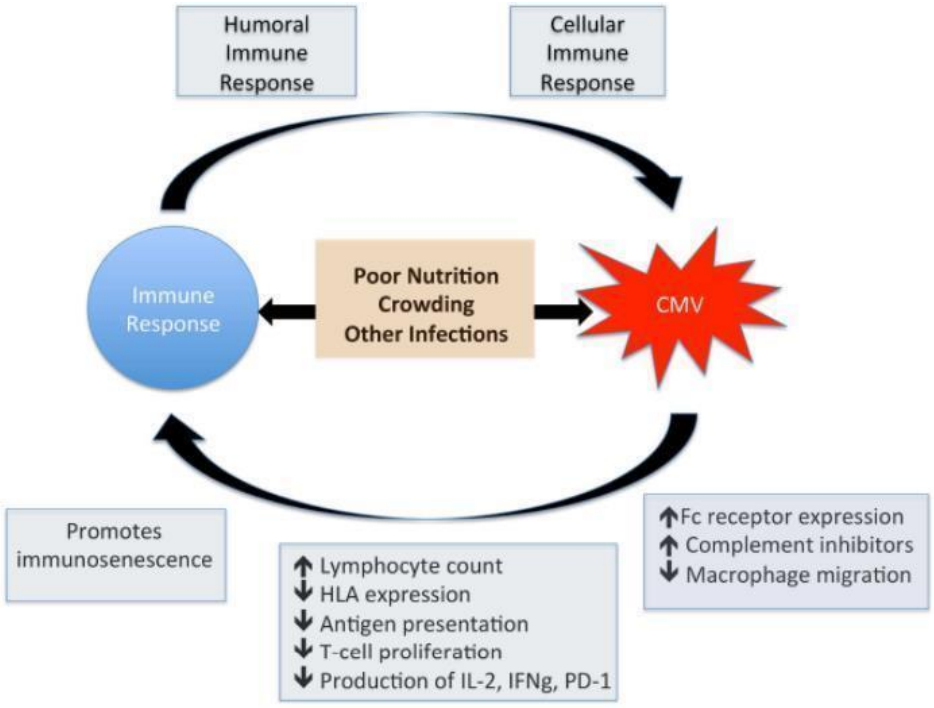

Figure 1: Impact of cytomegalovirus on the immune system (Adland and al. 2015)

Why it is important to do this review

Complex interactions exist between HIV and CMV, including a shared mode of in utero, perinatal, and post-natal routes of transmission (Doyle 1996; Guibert 2009); a higher rate of congenital CMV infection in HIV-infected infants (Doyle 1996; Guibert 2009); an impaired containment of CMV replication among HIV-infected infants (Slyker 2009); and a more severe course of HIV infection, accompanied by a higher rates of central nervous system complications (Kovacs 1999). Mortality is also higher in CMV-HIV co-infected infants (Slyker 2009), and poorer growth and development had been recorded even among HIV-exposed uninfected (HEU) infants who were co-infected with CMV (Gompels 2012; Anigilaje 2015). Whereby only minimal impact of HAART on breast milk CMV load was seen, suggesting that expanded maternal use of antiretroviral therapy may not reduce the risk of infant postnatal CMV acquisition via breast milk (Anigilaje 2015). Preventing or delaying CMV infection may represent a novel strategy to improve the health of both HIV-infected and HIV-exposed uninfected infants in sub–Saharan Africa, but requires a better understanding of CMV replication and transmission in the setting of maternal HIV-1. There are currently no ideal safe and effective interventions to reduce postnatal CMV infection (Filteau 2016). This review is focus on those issues and highlights different interactions between cytomegalovirus, HIV, antiretroviral therapy and breastfeeding.

Objectives

To investigate whether breastfeeding increase the risk of cytomegalovirus infection in HIV-exposed infants.

To evaluate whether antiretroviral therapy prophylaxis could decrease cytomegalovirus breastfeeding infection in postpartum.

Methods

Criteria for considering studies for this review

Types of studies

We included randomized control trials, non-randomized control trials and prospective cohort studies.

Types of participants

We included HIV-exposed infants, HIV-infected infants and HIV-infected women

Types of interventions

- Any breastfeeding was compared to no breastfeeding or formula feeding.
- Maternal antiretroviral therapy versus no maternal ARV or infants' prophylaxis.

Types of outcome measures

Primary outcomes

- Infant cytomegalovirus infection
- Time to CMV infection
- Time to screen CMV

Secondary outcomes

- All cause of mortality
- CMVIg G, CMV DNA and CMV PCR

Search methods for identification of studies

The following terms were searched: (Infants OR postnatal OR perinatal OR Infant OR fetus OR newborn OR fetal OR baby OR babies) OR (breastfeeding OR breast feeding OR exclusive breastfeeding OR exclusive breast feeding) AND (cytomegaloviruses OR cytomegalovirus OR CMV OR HCMV) AND (HIV OR "human immunodeficiency virus") AND (Highly Active Antiretroviral therapy OR HAART).

Electronic searches

Systematic electronic search was undertaken through:

- Cochrane Central Register of Controlled Trials (CENTRAL),
- Scorpus
- PubMed,
- LILACS
- Web of Science
- Clinicaltrials

Searching other resources

In addition, we performed hand searches in different website conferences, such as the International AIDS Conferences and the annual Conferences on Retroviruses and Opportunistic infections.

Data collection and analysis

Selection of studies

Two review authors (JT and EM) independently screened all titles and abstracts identified from searches to determine which met the inclusion criteria. We retrieved potentially relevant papers in full text. The same review authors independently screened full-text articles for inclusion or exclusion, with discrepancies resolved by discussion and by consulting a third review author where necessary to reach consensus. We planned to present reports of included studies. All excluded studies, with reasons for exclusion, are presented in Characteristics of excluded studies (table 2).

Data extraction and management

JT and EM independently extracted data using a data extraction form. In case of any disagreement between the two reviewers, JLT review author was consulted. We

extracted data using the following information:

Characteristics of trials:

- Study design
- calculation of sample size
- Bias assessment

Characteristics of participants:

- Number of participants enrolled (total, per study arm)
- Dropouts/withdrawals
- Inclusion criteria
- Exclusion criteria
- setting/country
- Age
- CD4 count
- Viral load

Characteristics of interventions

Characteristics of outcome measures

Characteristics of comparisons

Assessment of risk of bias in included studies

The quality of randomized controlled trials, non-randomized control trials and observational studies was assessed independently by the authors (J.T and L.M) using guidance from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Each domain of bias was judged as low, high or unclear. When there was divergence between the two authors, JLT was contacted as arbiter.

Measures of treatment effect

We performed analysis using Review Manager Software (RevMan 5). We used risk ratio and the odd ratio accordingly; its respective 95% confidence interval as summary measure of association was also calculated. We analyzed continuous data by using the mean differences, its standard deviations as well as its 95% confidence intervals.

Unit of analysis issues

We considered individual participants as the unit of analysis. We did not include any cross-over RCT as well as cluster-RCTs.

Dealing with missing data

We did not find any missing data among included studies.

Assessment of heterogeneity

We assessed heterogeneity using the Chi^2 test (we regarded a P-value of less than 0.10 as statistically significant) and l^2 statistic to estimate the degree of heterogeneity. I^2 of 25% was considered as low heterogeneity, 50% as moderate heterogeneity, and 75% as high heterogeneity.

Assessment of reporting biases

The review included less than ten studies, reporting biases were examined among risk of bias domains.

Data synthesis

Where included studies are sufficiently similar, we will conduct meta-analyses. We will carry out from fixed-effects meta-analysis. If heterogeneity is above 50%, we will perform random effects meta-analysis. The appropriate method of meta-analysis will be based on the nature of outcome data (dichotomous, ordinal, continuous, time-to-event etc). If outcome data in some studies to be combined are dichotomous and continuous in others, the dichotomous data will be re-expressed as standardized mean difference if the underlying continuous measurements in each intervention group follow a normal, enabling then data to be pooled.

Subgroup analysis and investigation of heterogeneity

When there was evidence of heterogeneity between the studies, we performed subgroup analyses focusing on: Randomized control trials and observational studies

Results

Results of the search

We found 1558 studies after removing duplicated papers, 1558 abstracts were screened and 1538 records were removed. We fully assessed 20 articles among which 9 were excluded with reasons. 11 papers were included as well as in qualitative and quantitative analysis (see figure 2).

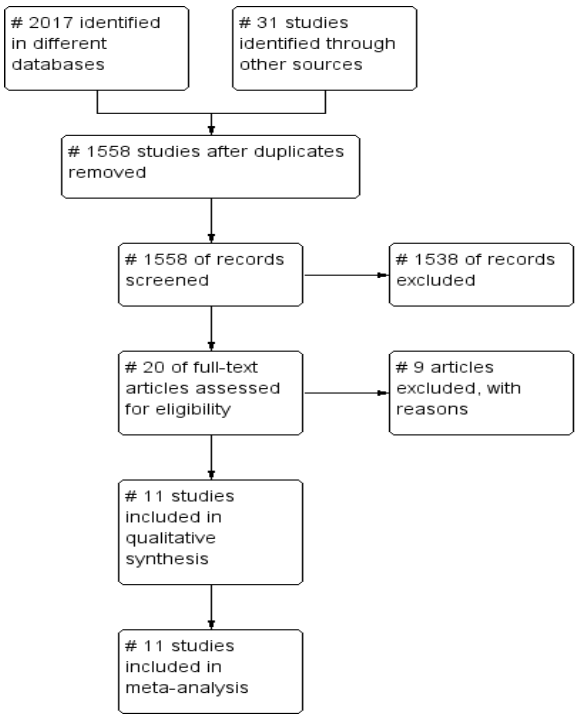

Figure 2: Study flow diagram.

Included studies

Included studies were discribed in Characteristics of included studies (see table 1). Ten studies were included in this review among which five RCTs (Chang 2015; Kourtis 2015; Richardson 2016; Roxby 2014; Slyker 2014) and six prospective cohort (Kfutwah 2017; Meyer 2014; Musonda 2016; Mussi-Pinhata 2009; Pirillo 2017; Slyker 2009).

Excluded studies

The characteristics of excluded studies were described in Characteristics of excluded studies (see table 2).

Risk of bias in included studies

Allocation (selection bias)

Sequence generation was low of bias risk in four RCTs (Chang 2015; Kourtis 2015; Richardson 2016; Roxby 2014), one RCT (Slyker 2014) was unclear. Therefore, sequence generation was not applicable in prospective cohort studies (Kfutwah 2017; Meyer 2014; Musonda 2016; Mussi-Pinhata 2009; Pirillo 2017; Slyker 2009). Allocation concealment was low of bias risk in (Richardson 2016), unclear in (Chang 2015; Kourtis 2015; Roxby 2014; Slyker 2014), supposed to be high risk of bias in prospective cohort studies.

Blinding (performance bias and detection bias)

Performance bias was low in on RCT (Roxby 2014), unclear in (Kfutwah 2017; Chang 2015; Kourtis 2015; Meyer 2014; Musonda 2016; Mussi-Pinhata 2009; Pirillo 2017; Slyker 2009; Slyker 2014) and high in (Richardson 2016). Therefore, detection bias was low of risk in all included studies.

Incomplete outcome data (attrition bias)

Attrition bias was minimized in all included studies.

Selective reporting (reporting bias)

Almost all studies reported low risk of bias in reporting bias, except (Mussi-Pinhata 2009) and (Pirillo 2017) where reporting bias was high and unclear respectively.

Other potential sources of bias

Mussi-Pinhata 2009 and Pirillo 2017 reported high potential sources of other bias.

Effects of interventions

1. Breastfeeding HIV-exposed infants were 77% more likely to have CMV infection compared to no breastfeeding and/or formula group (OR 0.23 95% CI (0.04 to 1.32), 5 studies, 1007 infants). Heterogeneity: $Tau^2 = 2.73$; $Chi^2 = 36.91$, df = 3 ($P < 0.00001$); $I^2 = 92\%$. This result was not statistically significant with p-value 0.10

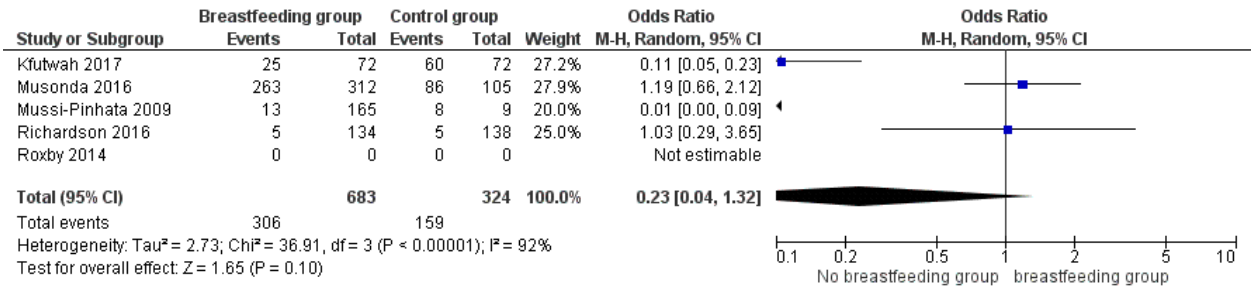

Figure 3: Forest of comparison: breastfeeding versus no breastfeeding: outcome: CMV infection.

2. Antiretroviral therapy reduced 83% of CMV infection compared to no antiretroviral therapy or antiretroviral prophylaxis (OR 0.17 95% CI 0.03 to 0.94, 3 studies, 560 infants), Heterogeneity: $Tau^2 = 2.16$; $Chi^2 = 31.10$, df = 2 ($P < 0.00001$); $I^2 = 94\%$. Test for overall effect: $Z = 2.03$ ($P = 0.04$)

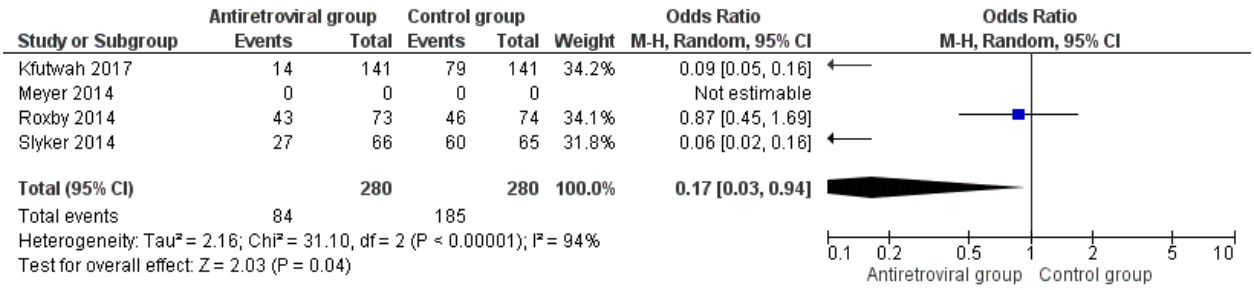

Figure 4: Forest plot of comparison: Antiretroviral versus control group: Outcome: CMV infection.

3. Breastfeeding HIV-exposed infants were 63% in risk of carrying CMV DNA compared to the control group. This result is shown as (OR 0.37 95% CI (0.20 to 0.67), 5 studies, 1823 infants), Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 14.78$, df = 4 ($P = 0.005$); $I^2 = 73\%$. Test for overall effect: $Z = 3.23$ ($P = 0.001$)

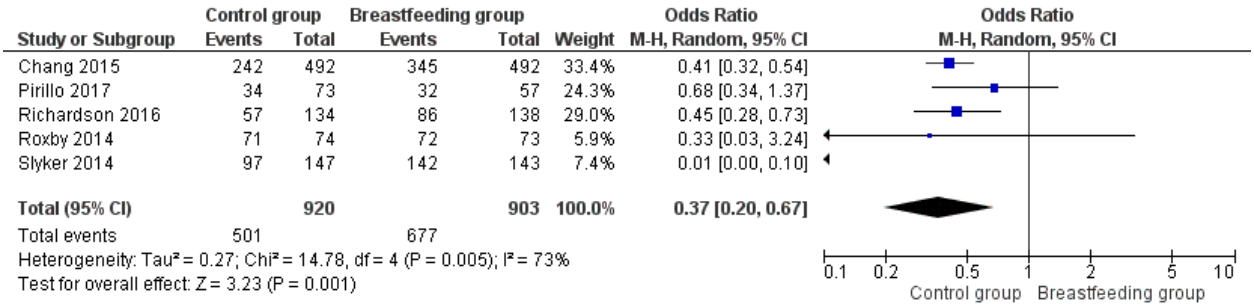

Figure 4: Forest plot of comparison: breastfeeding versus control groups: outcome: CMV infection.

4. The calculated mean difference of time to CMV infection between breastfeeding HIV-exposed infant group and control was 5.61 months 95% CI [5.34, 5.88]. We can conclude that breastfeeding increase the mean difference of time to CMV infection high as 5.34 months and as low as 5.88 months compared the control group. This result was highly statistically significant with Test for overall effect: Z = 40.86 (P < 0.00001).

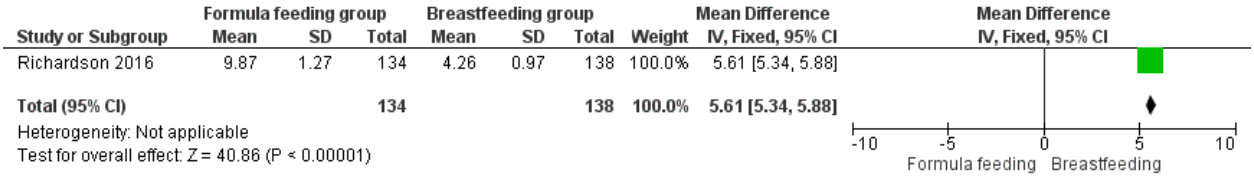

Figure 4: Forest plot of comparison: The mean difference of time of CMV infection: breastfeeding versus formula feeding.

5. In breastfeeding HIV-exposed infants, cytomegalovirus screening was 47% effective in >= 4 months compared to < 4 months of age (RR 1.47 95%CI 1.13 to 1.93, 1 study, 146 infants). Test for overall effect: Z = 2.82 (P = 0.005).

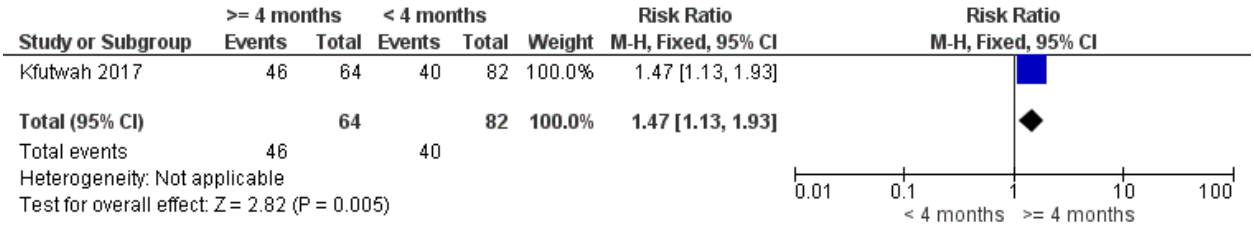

Figure 5: Forest plot of comparison: screening CMV infection: < 4 months versus >= 4 months

6. Breastfeeding HIV-exposed infants were 50 % in risk of carrying CMV IgG compared to the control group (OR 0.50 95% CI 0.30 to 0.84, 2 studies, 365 participants). Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df = 1 (P = 0.52); $I^2 = 0\%$, Test for overall effect: Z = 2.60 (P = 0.009)

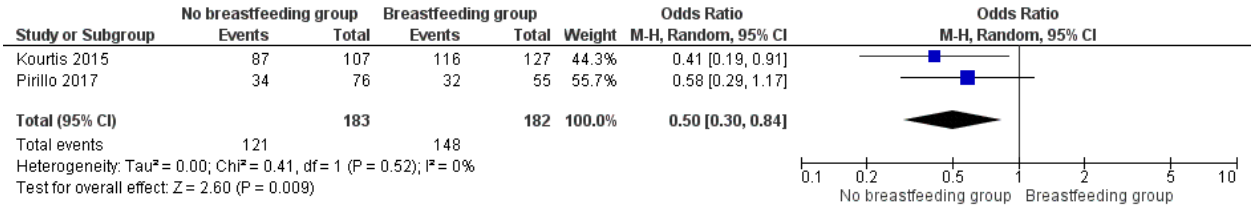

Figure 6: Forest plot of comparison: breastfeeding versus no breastfeeding: outcome: CMV IgG.

7. Breastfeeding HIV-exposed infants who were positive in CMV PCR were 42% in risk of dying compared to the compared group (RR 1.42 95% CI 0.57 to 3.57, 3 studies, 1426 infants). Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 8.16$, df = 2 (P = 0.02); $I^2 = 75\%$, Test for overall effect: Z = 0.75 (P = 0.46).

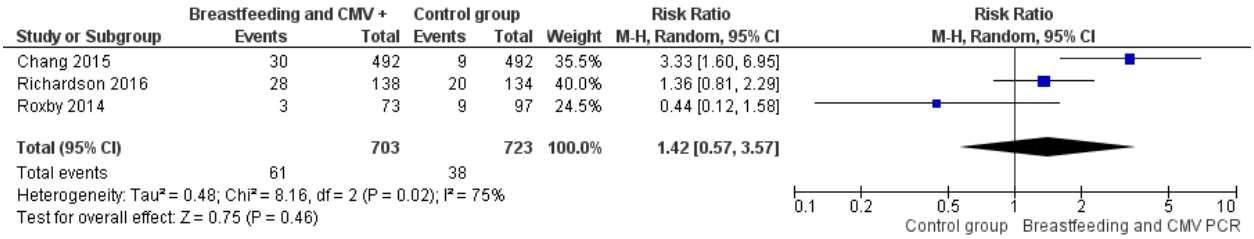

Figure 8

9. The test for subgroup differences did not shown significant difference between RCTs and observational studies in assessing CMV DNA outcome ($Chi^2 = 0.74$, df = 1 (P = 0.39), $I^2 = 0\%$).

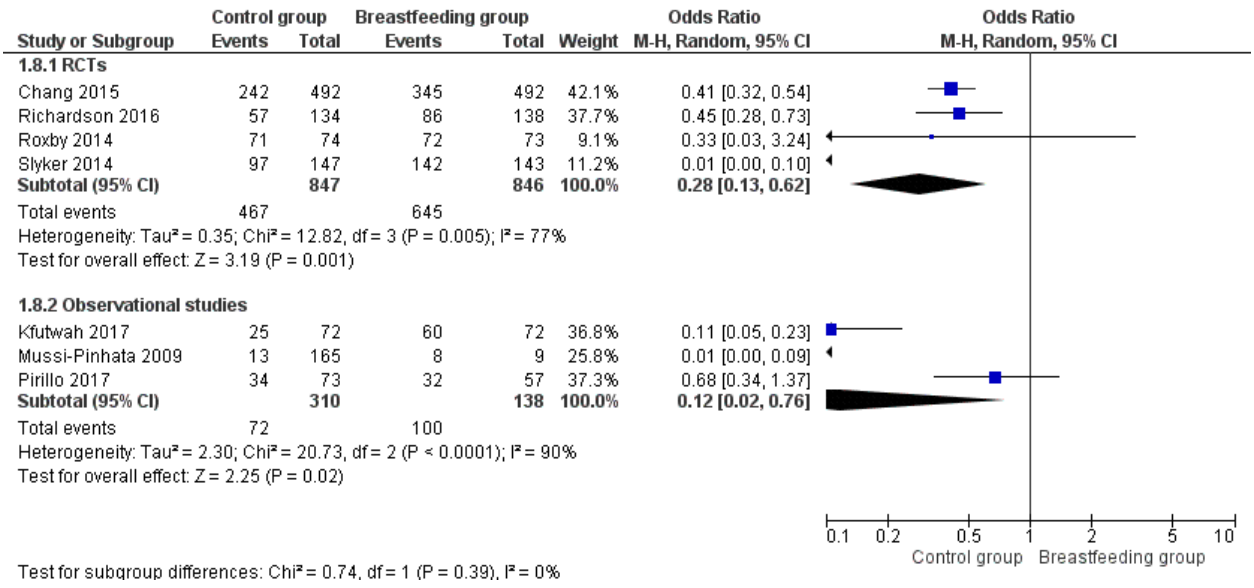

Figure 9:

The overall evidence was graded very low for CMV infection, CMV DNA and all cause of mortality. However, CMV screening was graded low; time to CMV infection CMV IgG were graded moderate (see table 3).

Discussion

Overall completeness and applicability of evidence

Breastfeeding is important for child survival and health, so switching from breastfeeding is not a feasible way to reduce transmission of CMV. This risk is largely unaffected by ART and is increased by breastfeeding, which itself is critically important for child health and survival (Filteau 2016). These HIV-exposed, uninfected (HEU) children are at increased risk of mortality and have immune, growth, development, and health deficits compared to HIV-unexposed children. HEU children are known to be at higher risk than HIV-unexposed children of acquiring cytomegalovirus (CMV) infection in early life. This risk is largely unaffected by ART and is increased by breastfeeding, which itself is critically important for child health and survival. Early CMV infection, namely in utero or during early infancy, may contribute to reduced growth, altered or impaired immune functions, and sensory and cognitive deficits. We review the evidence that CMV may be responsible for the health impairments of HEU children (Filteau 2016). Increased infections with maternal HIV exposure could result from maternal CMV reactivation, which is common in HIV-infected women, particularly with low CD4 counts; CMV was detected in the serum and cervix of, respectively, 4.8 and 66% ART-treated HIV-positive pregnant Kenyan women (Slyker 2014; Filteau 2016). A secondary analysis of a randomized controlled trial of breastfeeding versus formula-feeding by HIV-infected Kenyan women in the pre-ART era found that breastfeeding was associated with a significantly increased proportion of infants

CMV-infected by age 1 year (89 versus 69% in the formula group), as well as earlier median acquisition of CMV infection (4.26 versus 9.87 months) (Richardson 2016; Filteau 2016).

In this observational cohort study, maternal NFV during gestation was not associated with a reduction in the probability of CMV infection, nor with the quantity of CMV detected in plasma of infected infants (Gantt 2016). The proportion of infants with CMV infection did not differ significantly between the NFV-exposed and unexposed groups (Gantt 2016).

Quality of the evidence

The quality of the evidence was described in Summary of findings table 1. The outcome CMV infection was graded low because imprecision and an observational study (Musonda 2016) was included in meta-analysis. The evidence of CMV DNA in infants was graded as very low, therefore the time to CMV infection in infants had high evidence and both CMV IgG and all cause of mortality were graded as moderate.

Potential biases in the review process

This review included four prospective cohort studies. Selection bias commonly found in observational studies could impact on this study (see figure 10 and 11). Most of the results were subject to imprecision. We found also, heterogeneity was quite large in some forest plot. Lastly, the review included different types of comparisons inducing then indirectness.

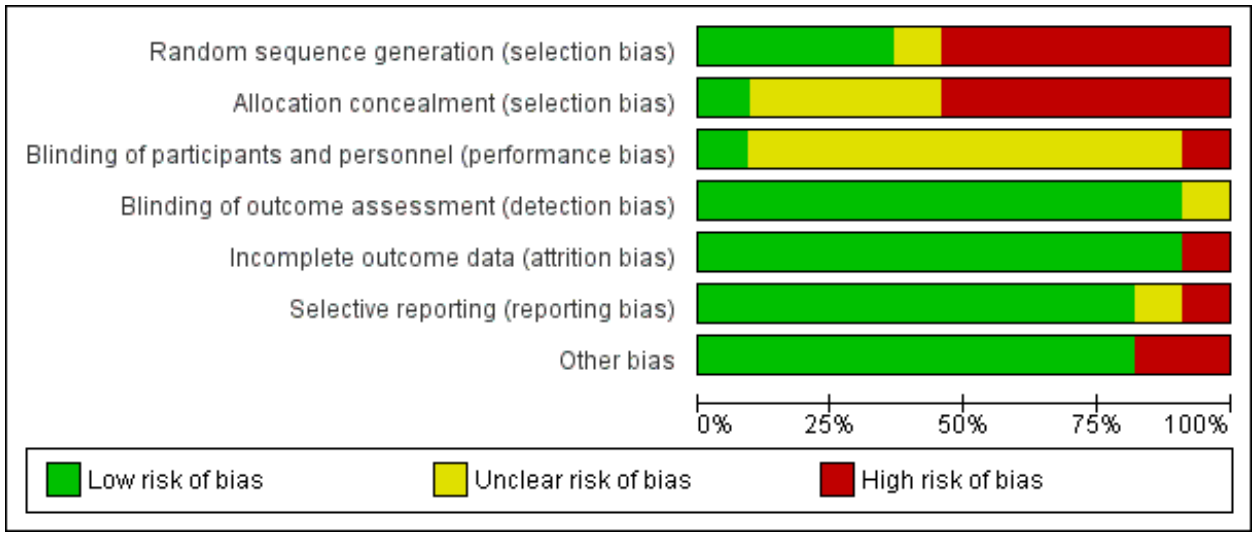

Figure 10: risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

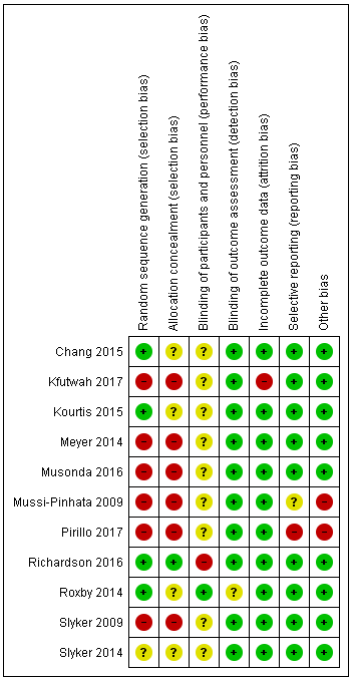

Figure 11: risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Agreements and disagreements with other studies or reviews

It is more difficult to assess any effects of maternal ART on postnatal CMV transmission, particularly in settings where breastfeeding is practiced, given generally very high rates of CMV transmission via breastfeeding (Filteau 2016; Ellington 2017) strengthened that co-infection CMV/HIV in infants requires a clinical trial of a safe and effective anti-CMV intervention in order to move forward. Another review suggested that treating breast milk from CMV-seropositive mothers would only be necessary until the infant reaches a certain age or birth weight, after which the risk of symptomatic CMV disease decreases (Lanzieri 2013).

Authors' conclusions

Implications for practice

CMV disease responds to treatment with a variety of antiviral agents including ganciclovir, valganciclovir, cidofovir, and foscarnet (Ellington 2017). In fact, appropriate diagnosis is challenging in resource-limited countries (Ellington 2017). Most common cases of post CMV is less diagnosed or completely ignored, and then disease is found out in complications stage. Effective actions should be undertaken to prevent CMV infection in developing countries. Further research are conducted to find out whether higher doses or novel anti-CMV drugs in the pipeline may offer opportunities to further investigate the effects of inhibition of CMV replication in HIV-infected mothers as a way to further decrease MTCT of both viruses and improve infant survival and health, particularly in resource-limited countries (Ellington 2017). This review has shown that the risk of catching CMV infection through breastfeeding is higher in HIV-exposed children. Maternal ART did have any effects on CMV transmission via breastfeeding. Knowing that exclusive breastfeeding until six months is crucial in preventing infectious diseases as well as metabolic diseases. Moreover, exclusive influences actively cognitive development. WHO urges exclusive breastfeeding until six months. In one hand, exclusive breastfeeding should be encouraged and improved, in the other hand, CMV should be prevented. As shown, the mean difference of time to CMV infection in HIV-exposed children is high as 5.34 months and as low as 5.88 months compared to non-exposed children. This study offers a perspective of preventing CMV infection in the last months of breastfeeding. Further

studies are needful to establish with antiviral such ganciclovir, valganciclovir, cidofovir and foscarnet could be used in HIV-exposed infants in the last months of exclusive breastfeeding. Other alternative such CMV vaccine should be investigated. A trial conducted with low dose (500 mg twice daily) of valacyclovir (GlaxoSmithKline) did not have any effect on the timing of infant CMV infection or breast milk CMV viral load (Roxby 2014; Filteau 2016). Recently, a trial comparing 6 months versus the standard 6 weeks of valganciclovir for congenital CMV infection found side effects in a proportion of infants: 19% of infants developed grade 3–4 neutropenia during the first 6 weeks of life that in three of 109 infants necessitated temporary suspension of treatment (Kimberlin 2015; Filteau 2016). A trial of hyperimmune globulin to prevent congenital CMV infection in infants of women with primary CMV infection found no significant decrease in congenital CMV infection, similar clinical outcomes among congenitally infected infants, and a higher rate of obstetric adverse events among the women treated with globulin compared to those given placebo (Revello 2014; Filteau 2016).

Implications for research

This review has shown CMV infection occurs frequently in breastfeeding HIV-exposed infants. This infection is more likely to happen in the last months of exclusive breastfeeding. However, maternal antiretroviral therapy could decrease significantly CMV infection in HIV-exposed children. In addition, this study illustrated that CMV should be screened above four months postnatal because CMV infection is acquired around five months post natal. Then we urge further research in this field so that CMV infection could be minimized in HIV-exposed infants in the last months of exclusive breastfeeding. Therefore, this review should be considered in a context of several limitations.

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Declarations of interest

Authors declare that they have no competing interests.

Published notes

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Annex tables

Tables 1: Characteristics of included studies

Chang 2015

Methods	randomized control trial, factorial design
Participants	Mother–infant pairs with HIV 1 infected mothers. 492 infants enrolled in the BAN (Breastfeeding, Antiretrovirals and Nutrition) study. Lilongwe, Malawi
Interventions	antiretroviral prophylaxis (maternal triple drug antiretroviral regimen vs. infant daily nevirapine administered during 28 weeks of breastfeeding vs. a control arm of only one week of antiretroviral prophylaxis).
Outcomes	At birth: CMV DNA in infants: 242/492 24 weeks of age(Breastfeeding): CMV DNA in infants: 345/492 48 weeks of age(No breastfeeding): CMV DNA in infants: 387/492 Infant death: 4.05 (0.51–32.0) HIV infection or infant death (2–48 weeks): 2.49 (0.86–7.21) HIV infection or infant death (24–48 weeks): 4.27 (0.99–18.4)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly selected from BAN subset...
Allocation concealment (selection bias)	Unclear risk	Information is not sufficient to judge "Yes" or "No"
Blinding of participants and	Unclear risk	Insufficient information to judge

personnel (performance bias)		
Blinding of outcome assessment (detection bias)	Low risk	Medical records were used to assess the outcome
Incomplete outcome data (attrition bias)	Low risk	Low rate of loss of follow up and balancing both sides
Selective reporting (reporting bias)	Low risk	Authors reported all pre-specified outcomes
Other bias	Low risk	

Kourtis 2015

Methods	randomized controlled clinical trial that evaluated, in a factorial design,
Participants	2,369 mother-infant pairs between 2004 and 2010 in Lilongwe, Malawi. We used stored infant plasma specimens from birth (28 specimens), 24 weeks of age (127 specimens), and 48 weeks of age (107 specimens), randomly selected from a subset of 492 BAN study infants
Interventions	antiretroviral prophylaxis (a maternal triple-drug antiretroviral regimen versus infant daily nevirapine administered during 28 weeks of breastfeeding versus a control arm of only 1 week of antiretroviral prophylaxis after delivery) and (ii) a maternal nutritional supplement during breastfeeding in reducing postnatal mother-to-child HIV transmission and enhancing maternal health during breastfeeding.
Outcomes	Infant CMV IgG levels and IgG avidity at birth and 24(breastfeeding) and 48 weeks(no breastfeeding) of age At Birth CMV IgG serology: 27/28 CMV PCR at 24 weeks CMV IgG positive (no. of samples): 116/127

	CMV PCR at 48 wks CMV IgG positive (no. of samples): 87 /107 CMV PCR results in the blood of HIV-exposed CMV PCR at 24 wks: 83/116 CMV PCR at 48 wks: 56/87
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	...randomly selected from a subset...
Allocation concealment (selection bias)	Unclear risk	Information provided is insufficient to judge "Yes" or "No"
Blinding of participants and personnel (performance bias)	Unclear risk	We do not have enough information to judge "Yes" or "No"
Blinding of outcome assessment (detection bias)	Low risk	IgG antibody against CMV was measured in plasma specimens using the vidas instrument
Incomplete outcome data (attrition bias)	Low risk	Loss of follow is balancing
Selective reporting (reporting bias)	Low risk	Even if the protocol is not available, therefore, all pre-specified outcomes were assessed.
Other bias	Low risk	The study appears to free of other bias

Meyer 2014

Methods	Prospective cohort study
Participants	Blantyre, Malawi
Interventions	Maternal antiretroviral use was assessed at each follow-up visit (delivery, 4–6 weeks, 3 months, and 6 months); untreated mothers and all infants were administered single dose Nevirapine at delivery. Mothers were counseled to exclusively breastfeed for the

	first six months and were provided with a peanut-based food supplement for their own nutrition for six months postpartum.
Outcomes	Maternal characteristics(IQR: interquartile range) Milk CMV DNA load (log10 copies/mL)b Treated group(n=16): 4.0 (3.2, 5.3) Untreated group(n=53): 4.0 (3.2, 4.6) Infant CMV acquisition Treated group(Antiretroviral therapy use): 2/16 Untreated group (Nevirapine): 1/53
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not applicable in prospective cohort studies
Allocation concealment (selection bias)	High risk	Not applicable in this study design
Blinding of participants and personnel (performance bias)	Unclear risk	Not enough information to judge 'Yes' or 'No'
Blinding of outcome assessment (detection bias)	Low risk	medical records were used to assess the outcome
Incomplete outcome data (attrition bias)	Low risk	Lost to follow up seems to be minimized
Selective reporting (reporting bias)	Low risk	All outcomes were reported and the study protocol is available
Other bias	Low risk	This study seems to be free of other types of bias

Musonda 2016

Methods	Two prospective cohort studies
Participants	Two hundred sixty-one HIV-infected and HIV-uninfected mothers were compared for HCMV deoxyribonucleic

	acid (DNA) loads and genotypes (glycoprotein gO) in milk from birth to 4 months postpartum. (2) Maternally HIV-exposed and HIV-unexposed infants were compared for HCMV infection risk factors. The second cohorts of 460 infants, from a trial of micronutrient fortified complementary-food to breastfeeding, were studied between 6 and 18 months of age. Studies were conducted at Chilenje clinic in Lusaka, Zambia, in 2 cohorts: in the first cohort, studies examined extended HCMV secretion in breast milk.
Interventions	Breastfeeding in HIV-infected women vs breastfeeding in HIV uninfected women.
Outcomes	HCMV DNA mothers in 16 weeks postpartum(milk) HIV-infected compared: 81/92 HIV-uninfected mothers:67/113 HCMV Infant Infection (Antibody): HIV-Positive Mothers: 86/ 105 HIV-Negative Mothers: 263/312
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not applicable for cohort study
Allocation concealment (selection bias)	High risk	Not applicable for cohort study
Blinding of participants and personnel (performance bias)	Unclear risk	Information were not provided
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessment was done through laboratory records
Incomplete outcome data (attrition bias)	Low risk	Lost to follow up was minimized
Selective reporting (reporting bias)	Low risk	The study was registered with ID: ISRCTN37460449
Other bias	Low risk	This study seems to be free of other

	bias

Mussi-Pinhata 2009

Methods	Prospective cohort study
Participants	Two study groups were composed: group 1 consisted of 150 HIV-1-seropositive mothers and their infants seen from June 30, 1992, to December 30, 1995; group 2 consisted of 175 HIV-1-seronegative mothers and their infants seen from March 1994 to August 1995.The study was conducted on mother-infant pairs seen at the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil, which provides care for a low-income population.
Interventions	HIV exposed infants were compared to non-exposed. We considered breastfeeding infants in both groups. Follow-up at the outpatient clinic was provided by the authors at the same hospital. Routine visits were scheduled for 15 days, 1 month, and 2, 3, 4, 5, 6, 9, 12, and 18 months of age. Developmental and morbidity data were obtained during each visit.
Outcomes	CMV infection Exposed infants: 8/9 Non exposed infants: 13/165
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Random sequence generation was not applicable
Allocation concealment (selection bias)	High risk	Random sequence generation was not applicable
Blinding of participants and personnel (performance bias)	Unclear risk	We were unable to judge 'Yes' or 'No'
Blinding of outcome assessment (detection bias)	Low risk	Laboratory records were used to assess the outcome

Incomplete outcome data (attrition bias)	Low risk	Lost to follow up was minimized in statistical analysis by using respective group sample size
Selective reporting (reporting bias)	Unclear risk	We could not judge because of lack of information
Other bias	High risk	Confounding were not controlled

Pirillo 2017

Methods	Prospective cohort study
Participants	A cohort of 89 HIV-infected mothers and their children was studied. Women received antiretroviral therapy from week 25 of gestation until 6 months postpartum or indefinitely if meeting the criteria for treatment. The study was conducted in Malawi. HIV-infected women received from week 25 of gestation a combination of antiretroviral drugs based on either stavudine or zidovudine, and lamivudine and nevirapine and continued it until 6 months after delivery if not meeting the criteria for treatment at the time of the study (baseline CD4 >350/mm3) or indefinitely if in need for their own health (CD4+ <350/ mm3).
Interventions	Women received antiretroviral therapy from week 25 of gestation until 6 months postpartum or indefinitely if meeting the criteria for treatment. The recommendation was for a 6-month period of exclusive breastfeeding.
Outcomes	All infants Anti-CMV/IgM+: Month 1: 8/86 Month 6: 2/ 33 Month 12: 4/74 Month 24(Anti-CMV/IgG+): 80/83 CMV DNA+ Month 6: 34/ 56

	Month 12: 39/82 HIV-exposed uninfected infants Anti-CMV/IgM+ Month 1: 7/81 Month 6: 1/ 31 Month 12: 2/72 Month 24(Anti-CMV/IgG+): 76/79 CMV DNA+ Month 6: 32/55 Month 12: 34/76 HIV-infected infants Anti-CMV/IgM+ Month 1: 1/4 Month 6: 1/2 Month 12: 2/ 2 Month 24(Anti-CMV/IgG+): 4/ 4 CMV DNA+ Month 6: 0/1 Month 12: 5/6
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	High risk	This is a prospective cohort study, random sequence generation is not applicable
Allocation concealment (selection bias)	High risk	This is a prospective cohort study, allocation concealment is not applicable
Blinding of participants and personnel (performance bias)	Unclear risk	Not enough information to judge 'Yes' or 'No'
Blinding of outcome assessment (detection bias)	Low risk	The outcome was assessed by laboratory records
Incomplete outcome data (attrition bias)	Low risk	Lost to follow up was minimized
Selective reporting (reporting bias)	Low risk	The protocol is not available, therefore, all outcomes were reported
Other bias	High risk	...the small sample size

Richardson 2016

Methods	randomized controlled trial
Participants	HIV-infected women in Nairobi, Kenya. A total of 138 breastfed and 134 formula-fed infants underwent CMV testing.
Interventions	Median duration of breastfeeding was 14 months. Infants had a median of 11 study visits in the breastfeeding arm and 13 study visits in the formula feeding arm.
Outcomes	CMV infected at birth Breastfeeding Arm: 5/138 Formula-Feeding Arm: 5/134 CMV DNA positive Breastfeeding Arm: 86/138 Formula-Feeding Arm: 57/134 CMV DNA negative and serology positive Breastfeeding Arm: 25/138 Formula-Feeding Arm: 24/134

	CMV DNA or serology positive Breastfeeding Arm: 111/138 Formula-Feeding Arm: 81/134 Time to CMV infection, No, median ± SE Breastfeeding Arm: 4.26 ± 0.97/138 Formula-Feeding Arm: 9.87 ± 1.27/134 Infant died Breastfeeding Arm: 28/138 Formula-Feeding Arm: 20/134
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	...women were randomly assigned to the breastfeeding or formula-feeding arm at a 1:1 ratio, using computer-generated block randomization.
Allocation concealment (selection bias)	Low risk	...assignment to study arm was revealed to women and clinicians via pre-sealed envelopes.
Blinding of participants and personnel (performance bias)	High risk	Treatment allocation was not blinded to study staff…
Blinding of outcome assessment (detection bias)	Low risk	All CMV loads were measured in DBS as previously described
Incomplete outcome data (attrition bias)	Low risk	All analyses were intent-to-treat...
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were assessed.
Other bias	Low risk	This study seems to be free of other types of bias.

Roxby 2014

Methods	randomized double-blind, placebo-controlled clinical trial (RCT)
Participants	147 women consented to CMV testing; a total of 141 infants underwent CMV testing. All mothers received PMTCT. 74 HIV-infected women in intervention group and 74 in control group. 278 breast milk specimens in intervention group and 264 in control group. 71 HIV-exposed infants tested for CMV in intervention group and 70 in control group. Nairobi from April 2008 to June 2009/ Kenya
Interventions	500 mg twice-daily valacyclovir or placebo for 12 months. Infants were breastfed.
Outcomes	Cervical CMV DNA tested at 38 weeks Intervention group: 50/73 Control group: 49/74 Breast milk CMV DNA tested Intervention group: 72/73 Control group: 71/74 Acquired CMV Intervention group:47/73 Control group: 46/74 Infant deaths Intervention group: 3/73 Control group: 9/74
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	...independent statistician generated random sequentially-numbered study identifiers using a 1:1 allocation scheme with block sized of 20.
Allocation concealment (selection bias)	Unclear risk	We do not have enough information to judge 'Yes' or 'No'
Blinding of participants and personnel (performance bias)	Low risk	Participants were sequentially enrolled and no staff at the study site had knowledge of any participant allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	Medical records were used to assess outcomes.
Incomplete outcome data (attrition bias)	Low risk	Intention to treat was used Statistical Methods.
Selective reporting (reporting bias)	Low risk	The protocol was registered (http://clinicaltrials.gov NCT00530777)
Other bias	Low risk	This study seems to be free of other type of bias.

Slyker 2009

Methods	Prospective cohort study
Participants	Sixty-four infants were selected from the larger cohort based on survival to at least 3 months of age and the availability of a plasma specimen by 1 month of age. Infants were followed until death or exit from the study at 1 year (HIV-exposed uninfected) or 2 years of life (HIV infected). A cohort of infants born to HIV-infected women was used to study acute infant CMV infection.
Interventions	The women received short-course zidovudine for prevention of HIV-1 transmission. CMV plasma viral loads were serially measured in 20 HIV-exposed uninfected and 44 HIV-infected infants born to HIV-infected mothers.
Outcomes	CMV DNA

	At birth HIV-infected infants: 41/44 HIV-exposed uninfected infants: 18/20 Peripartum HIV-infected infants: 12/16 HIV-exposed uninfected infants: 6/20 Breastfeeding HIV-infected infants: 11/44 HIV-exposed uninfected infants: 4/20
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Random sequence generation was not conducted
Allocation concealment (selection bias)	High risk	Allocation concealment is not applicable
Blinding of participants and personnel (performance bias)	Unclear risk	Not specified in the study
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessment was done through laboratory records
Incomplete outcome data (attrition bias)	Low risk	Lost to follow was reduced
Selective reporting (reporting bias)	Low risk	Study protocols were approved by the Ethics Review Committee of Kenyatta National Hospital and the Institutional Review Board of the University of Washington.
Other bias	Low risk	The study seems to be free of other bias

Slyker 2014

Methods	Parallel randomized control trial
Participants	147 HIV/herpes simplex virus type 2 co-infected women were recruited at 28–32 weeks gestation. The PMTCT regimen consisted of twice-daily zidovudine from 28 weeks, zidovudine every 3 hours during labor until delivery, and single-dose nevirapine at the onset of labor.
Interventions	Women were randomized to twice-daily valacyclovir at 500 mg or placebo and continued until 1 year postpartum.
Outcomes	CMV DNA levels Maternal cervix: n = 97/147 breast milk of women n = 142/143 CMV Acquisition in HIV-1–Exposed Infants: Valacyclovir group: 27/66 Control group: 60/65
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Difficult to judge 'Yes' or 'No'
Allocation concealment (selection bias)	Unclear risk	Information provided is not sufficient to judge this domain.
Blinding of participants and personnel (performance bias)	Unclear risk	We do not have enough information to judge "Yes" or "No"
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were assessed through medical records
Incomplete outcome data (attrition bias)	Low risk	Lost to follow up was minimized to affect the results.
Selective reporting (reporting bias)	Low risk	The protocol is registered with this reference number NCT00530777
Other bias	Low risk	The study appears to be free of other types of bias.

Table 2: Characteristics of excluded studies

Anigilaje 2015	
Reason for exclusion	Cross-sectional study
Adland 2015	
Reason for exclusion	Review of literature
Reason for exclusion	Descriptive study
Gantt 2016	
Reason for exclusion	Cross-sectional study
Gompels 2012	
Reason for exclusion	The intervention was not directly included in the study
Khamduang 2011	
Reason for exclusion	Case control study
Slyker 2009a	
Reason for exclusion	Outcomes assessed were different than those included in the study
Stowell 2014	
Reason for exclusion	Cross-sectional study

Viljoen 2015

Reason for exclusion	Case control study

Table 3: Summary of findings tables

Breastfeeding compared to Standard care for Cytomegalovirus infection in HIV-exposed infants

Breastfeeding for Cytomegalovirus transmission in HIV-exposed infants				
Patient or population: patients with Cytomegalovirus transmission in HIV-exposed infants Settings: Malawi, Kenya, Cameroun, Zambia and Brazil Intervention: Breastfeeding				
Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Breastfeeding			
CMV infection	Study population	OR 0.23 (0.04 to 1.32)	1007 (5 studies)	⊕⊖⊖⊖ very low[1,2,3,4]	
	491 per 1000	181 per 1000 (37 to 560)			
	Moderate				
	826 per 1000	522 per 1000 (160 to 862)			
CMV infection	Study population	OR 0.17 (0.03 to 0.94)	560 (3 studies)	⊕⊖⊖⊖ very low[5,6,7]	
	661 per 1000	249 per 1000 (55 to 647)			
	Moderate				
	591 per 1000	197 per 1000 (42 to 576)			
Time to CMV infection		The mean time to cmv infection in the intervention groups was 5.61 higher (5.34 to 5.88 higher)	272 (1 study)	⊕⊕⊕⊖ moderate[8]	
Age of screening	Study population	RR 1.47 (1.13 to 1.93)	146 (1 study)	⊕⊕⊖⊖ low[9,10]	
	488 per 1000	717 per 1000 (551 to 941)			
	Moderate				
	488 per 1000	717 per 1000 (551 to 942)			
CMV	Study population	OR 0.37	1823	⊕⊖⊖⊖	

DNA in infants	750 per 1000	526 per 1000 (375 to 667)	(0.2 to 0.67)	(5 studies)	very low[11,12,13]
	Moderate				
	833 per 1000	649 per 1000 (499 to 770)			
CMV IgG	Study population		OR 0.5	365	⊕⊕⊕⊖
	813 per 1000	685 per 1000 (566 to 785)	(0.3 to 0.84)	(2 studies)	moderate[14]
	Moderate				
	748 per 1000	597 per 1000 (471 to 714)			
All cause of mortality	Study population		RR 1.42	1426	⊕⊖⊖⊖
	53 per 1000	75 per 1000 (30 to 188)	(0.57 to 3.57)	(3 studies)	very low[15,16,17]
	Moderate				
	93 per 1000	132 per 1000 (53 to 332)			

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 3 observational studies were included (Kfutwah 2017; Musonda 2016; Mussi-pinhata 2009)
[2] Heterogeneity was high
[3] Different comparisons were included
[4] the 95 %CI was large enough and included the null value.
[5] Observational studies were included
[6] Heterogeneity was high between studies.
[7] Different types of interventions and comparisons were included.
[8] Participants and personnel were not blind.
[9] Observational study is more likely of selection bias
[10] the risk ratio was above 1
[11] Observational studies were included in the analysis
[12] Heterogeneity between studies was large.
[13] Different types of comparison were included.

[14] An observational study was included.
[15] Heterogeneity was above 60 %.
[16] Comparisons were quite different
[17] the 95% CI was large enough and included the null value.