ClinicalEvidence

HIV: mother-to-child transmission

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ABSTRACT

INTRODUCTION: Over 2 million children are thought to be living with HIV/AIDS worldwide, of whom over 80% live in sub-Saharan Africa. Without anti-retroviral treatment, the risk of HIV transmission from infected mothers to their children is 15–30% during gestation or labour, and 15–20% during breast feeding. HIV-1 infection accounts for most infections; HIV-2 is rarely transmitted from mother to child. Transmission is more likely in mothers with high viral loads and/or advanced disease, in the presence of other sexually transmitted diseases, and with increased exposure to maternal blood. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of measures to reduce mother to child transmission of HIV? We searched: Medline, Embase, The Cochrane Library and other important databases up to January 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). We performed a GRADE evaluation of the quality of evidence for interventions. RESULTS: We found 18 systematic reviews, RCTs, or observational studies that met our inclusion criteria. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antiretroviral drugs, different methods of infant feeding, elective caesarean section, immunotherapy, vaginal microbicides, and vitamin supplements.

QUESTIONS

INTERVENTIONS

Key points

- Without active intervention, the risk of mother-to-child transmission (MTCT) of HIV-1 is high, especially in populations where prolonged breast feeding is the norm.

  Without antiviral treatment, the risk of transmission of HIV from infected mothers to their children is approximately 15–30% during pregnancy and labour, with an additional 10–20% transmission risk attributed to prolonged breast feeding.

  HIV-2 is rarely transmitted from mother to child.

  Transmission is more likely in mothers with high viral loads and/or advanced HIV disease.

  Without antiretroviral treatment (ART), 15–30% of vertically infected infants die within the first year of life.

  The long-term treatment of children with ART is complicated by multiple concerns regarding the development of resistance, and adverse effects.

  From a paediatric perspective, successful prevention of MTCT remains the most important focus.

- Antiretroviral drugs given to the mother during pregnancy or labour, and/or to the baby immediately after birth, reduce the risk of MTCT of HIV-1.

- Reductions in MTCT are possible using simple ART regimens.

  Longer courses of ART are more effective, but the greatest benefit is derived from treatment during late pregnancy, labour, and early infancy.

  Suppression of the maternal viral load to undetectable levels (below 50 copies/mL) using highly active antiretroviral therapy (HAART) offers the greatest risk reduction, and is currently the standard of care offered in most resource-rich countries, where MTCT rates have been reduced to 1–2%.

  Alternative short-course regimens have been tested in resource-limited settings where HAART is not yet widely available. RCTs demonstrate that short courses of antiretroviral drugs have proven efficacy for reducing MTCT. Identifying optimal short-course regimens (drug combination, timing, and cost effectiveness) for various settings remains a focus for ongoing research.

- Avoidance of breast feeding prevents postpartum transmission of HIV, but formula feeding requires access to clean water and health education.

The risk of breast feeding-related HIV transmission needs to be balanced against the multiple benefits that breast feeding offers. In resource-poor countries, breast feeding is strongly associated with reduced infant morbidity and improved child survival.

Modified breastfeeding practices may reduce the risk of HIV transmission while retaining some of its associated benefits.

In settings where formula feeding is not feasible (no clean water, insufficient health education, significant cultural barriers) modified breastfeeding practices may offer the best compromise.

Early breast feeding with weaning around age 4–6 months may offer an HIV-free survival benefit compared with either formula, mixed feeding, or prolonged breast feeding.

Heat- or microbicidal-treated expressed breast milk may offer value in particular settings.

- Elective caesarean section at 38 weeks may reduce vertical transmission rates (apart from breast-milk transmission).

  The potential benefits of this intervention need to be balanced against the increased risk of surgery-associated complications, high cost, and feasibility issues. These reservations are particularly relevant in resource-limited settings.

- Immunotherapy with HIV hyperimmune globulin or immunoglobulin without HIV antibody does not reduce HIV-1 MTCT risk.
- Vaginal microbiocides have not been demonstrated to reduce HIV-1 MTCT risk.
- There is no evidence that vitamin A or multivitamin supplementation reduces the risk of HIV-1 MTCT or infant mortality.

DEFINITION

Mother to child transmission (MTCT) of HIV infection is defined as transmission of HIV from an infected mother to her child during gestation, labour, or postpartum through breast feeding. HIV-1 infection is frequently transmitted from mother to child, [1] although HIV-2 is rarely transmitted in this way. [2] Infected children rarely have symptoms or signs of HIV at birth, but usually develop them over subsequent months. [3]

INCIDENCE/ PREVALENCE

A review of 13 cohort studies estimated the risk of MTCT of HIV in the absence of anti-retroviral treatment (ART), to be 15–20% in Europe, 15–30% in the USA, and 25–35% in Africa. [4] The risk of transmission is estimated to be 15–30% during pregnancy, with an additional transmission risk of 10–20% associated with prolonged breast feeding. [5] The Joint United Nation's Programme on HIV/AIDS (UNAIDS) estimates that more than 2 million children are infected with HIV-1 worldwide, and that more than 1800 new HIV infections are transmitted daily from mothers to infants. [6] Of these, more than 80% are in sub-Saharan Africa, where more than 500,000 children were newly infected with HIV in 2004 alone. [6]

AETIOLOGY/ RISK FACTORS

Transmission of HIV to infants is more likely if the mother has a high viral load. [1] [7] [8] A Tanzanian study reported that a viral load of 50,000 copies/mL or more at delivery was associated with a 4-fold increase in the risk of early transmission, using polymerase chain reaction (PCR) results at 6 weeks of age (OR 4.21, 95% CI 1.59 to 11.13; P = 0.004). [9] Other maternal risk factors include sexually transmitted diseases, chorioamnionitis, prolonged rupture of membranes, vaginal mode of delivery, low $CD4^+$ count, advanced maternal HIV disease, obstetric events with bleeding (episiotomy, perineal laceration, and intrapartum haemorrhage), young maternal age, and history of stillbirth. [6] [10] [11] [12] [13] [14] A recent multi-centre RCT, conducted in Africa to investigate the ability of a simple anti- and peripartum antibiotic regimen to reduce the incidence of chorioamnionitis and the associated risk of MTCT of HIV-1, failed to demonstrate any protective effect (proportions of HIV-infected children at birth; antibiotics 7%, placebo 8%; P = 0.41). [15] Estimations of the timing of MTCT of HIV-1 during pregnancy indicate that the vast majority of transmission (80%) occurs during late pregnancy (3% at less than 14 weeks, 3% at 14–28 weeks, 14% at 28–36 weeks, 50% at 36 weeks to labour, and 30% during labour). [16] Prolonged breast feeding poses a significant additional risk for MTCT, with about 60% of total transmissions occurring during pregnancy, and 40% via breast milk, in breastfeeding populations. [16] [17] With the use of effective drug regimens to reduce peri-partum MTCT of HIV, prolonged breast or mixed feeding becomes the predominant route of transmission. [16] Late postnatal transmission (beyond 3–6 months) contributes substantially to overall MTCT; this may occur throughout the total period of breast feeding. [18] [17]

PROGNOSIS

The natural history of HIV infection in infancy is variable. It has been estimated that 25% of infants infected with HIV progress rapidly to AIDS or death within the first year of life, although some survive beyond 12 years of age even in the absence of ART. [3] A collaborative European study that documented the natural history of disease in the absence of ART, reported 15% mortality during infancy, and 28% mortality by the age of 5 years. [3] [19] However, the prognosis of African children with vertically acquired HIV infection may be worse. In a prospective study conducted in Kigali, Rwanda, the cumulative probability of death in 54 HIV-infected children was 0.26 (95% CI 0.16 to 0.41) at

1 year, 0.45 (95% CI 0.32 to 0.60) at 2 years, and 0.62 (95% CI 0.47 to 0.78) at 5 years. [20] In comparison, the cumulative probability of death in HIV-uninfected children at 5 years of age was 15 times less (0.04, 95%CI: 0.02 to 0.07). [18] Among the HIV-infected children, the cumulative probabilities of developing AIDS were 0.17, 95% CI 0.09 to 0.32 at 1 year, 0.28, 95% CI 0.17 to 0.45 at 2 years, and 0.35, 95%CI 0.22 to 0.53 at 5 years of age. Of the 28 HIV-infected children that died, 9 met the case definition of AIDS. On a population level, HIV accounted for 2% of deaths in 1990, and almost 8% in 1999, in children under 5 years of age living in sub-Saharan Africa. [21] Five countries (Botswana, Namibia, Swaziland, Zambia, and Zimbabwe) reported HIV-attributable mortality rates in excess of 30/1000 in children under the age of 5 years.

AIMS OF INTERVENTION To reduce MTCT of HIV and improve infant survival, with minimal adverse effects.

OUTCOMES HIV infection status of the child; infant morbidity and mortality; adverse effects in mothers and/or infants.

METHODS *BMJ Clinical Evidence* search and appraisal January 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2007, Embase 1980 to January 2007, the Cochrane Database of Systematic Reviews 2007, Issue 1, and Cochrane Central Register of Controlled Clinical Trials 2006, Issue 4. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, including open trials, and containing any number of individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 20).

QUESTION What are the effects of measures to reduce mother-to-child transmission of HIV?

OPTION ANTIRETROVIRAL DRUGS

HIV infection

Antiretrovirals compared with placebo in a breastfeeding population Zidovudine administered during the perinatal period starting from 36 weeks' gestation may be more effective than placebo at reducing MTCT of HIV infection in women who breastfeed (low-quality evidence).

Antiretrovirals compared with placebo in a non-breastfeeding population A long course of zidovudine given to mothers in the antepartum period (from 14 weeks' gestation), in the intrapartum period, and to infants for up to 6 weeks is more effective than placebo at reducing HIV infection in infants at 18 months in women who do not breastfeed (moderate-quality evidence).

Longer regimens compared with shorter regimens using the same antiretrovirals in a breastfeeding population In women who breastfeed, longer regimens of zidovudine given to mothers only and shorter regimens given to mothers during labour, and to infants for 3 days after birth seem to be equally effective at reducing the risk of HIV infection in infants at 4 weeks to 18 months (high-quality evidence).

Longer regimens compared with shorter regimens using the same antiretrovirals in a non-breastfeeding population We don't know whether longer regimens of the same antiretrovirals are more effective than shorter regimens at reducing MTCT of HIV infection in women who do not breastfeed. It seems that zidovudine given earlier to mothers only (starting from 28 weeks' gestation) is more effective than zidovudine given to mothers later (starting from 36 weeks) plus given to infants for 6 weeks after birth at reducing MTCT of HIV infection at 6 months (moderate-quality evidence).

Regimens using different drugs and durations of treatment in a breastfeeding population We don't know whether one zidovudine, or nevirapine regimen, and duration of treatment is more effective than the others at reducing the risk of HIV infection in infants at 4 weeks to 18 months (low-quality evidence).

Regimens using different drugs and durations of treatment in a non-breastfeeding population We don't know whether one zidovudine, or nevirapine or other antiretroviral regimens, and duration of treatments are more effective than the others at reducing the risk of HIV infection in infants at 4 weeks to 6 months (low-quality evidence).

Infant mortality

Antiretrovirals compared with placebo in a breastfeeding population Zidovudine administered during the perinatal period starting from 36 weeks' gestation may be no more effective than placebo at reducing infant mortality at 18 months in women who breastfeed (low-quality evidence).

Antiretrovirals compared with placebo in a non-breastfeeding population Zidovudine given to mothers alone in the antepartum period (14–38 weeks' gestation), in the intrapartum period, during labour and to infants for up to 6 weeks is no more effective than placebo at reducing infant mortality at 6–18 months in women who do not breastfeed (low-quality evidence).

Longer regimens compared with shorter regimens using the same antiretrovirals in a breastfeeding population In breastfeeding women, longer regimens of zidovudine given to mothers only (starting from 36 weeks' gestation) in the intrapartum period, and during labour and shorter regimens given to mothers during labour, and to infants for 3 days seem to be equally effective at reducing infant mortality at 4 weeks to 12 months (moderate-quality evidence).

Longer regimens compared with shorter regimens using the same antiretrovirals in a non-breastfeeding population We don't know whether zidovudine given to mothers (starting from 28 weeks' gestation) is more effective than zidovudine given to mothers (starting from 36 weeks) and to infants for 6 weeks at reducing infant mortality at 6 months (moderate-quality evidence).

Regimens using different drugs and durations of treatment in a breastfeeding population We don't know whether one zidovudine, or nevirapine regimen, and duration of treatment is more effective than the others at reducing infant mortality at 4 weeks to 18 months (low-quality evidence).

Regimens using different drugs and durations of treatment in a non-breastfeeding population We don't know whether one zidovudine, nevirapine or other antiretroviral regimens, and duration of treatments are more effective than the others at reducing the risk of mortality in infants at 4 weeks to 6 months (very low-quality evidence).

Note

For HIV-infected women who present late for delivery, post-exposure ART prophylaxis limited to babies may be valuable. The use of these short-course regimens has not been associated with short-term safety concerns. However, the potential long-term harm of selecting drug-resistant mutations is a serious concern.

For GRADE evaluation of interventions for HIV: mother-to-child transmission, see table, p 20 .

Benefits:

We found one systematic review (search date 2006,18 RCTs, 14,398 people), [22] and two subsequent RCTs. [23] [24] For full details of the RCTs, see table 1, p 13 , which presents a comprehensive overview of the individual RCTs by publication date. For the review, the primary outcome assessed was the relative risk reduction in HIV transmission rate at various time-points, based on survival analysis. The published transmission rates were used, and where not available the authors of the review calculated the transmission rates using published data. Efficacy, at a specific time point, was defined as the relative risk reduction in the proportion of infants infected.

Antiretrovirals versus placebo in a breastfeeding population:

The systematic review identified three RCTs. [25] [26] [27] The first RCT found that zidovudine given to mothers only, from 36 weeks' gestation and in labour, significantly reduced HIV infection in infants at 4–8 weeks and at 3–4 months compared with placebo. [25] The RCT also found that zidovudine significantly decreased infant mortality at 1 week and at 3–4 months compared with placebo, but found no significant difference in stillbirth between groups. The second RCT found that zidovudine given to mothers only, from 36–38 weeks' gestation, in labour, and for 7 days after delivery, significantly reduced HIV infection in infants at up to 18 months. [26] However, the RCT found no significant difference in infant mortality at up to 18 months, or in stillbirth. The third RCT compared four treatments: zidovudine plus lamivudine from 36 weeks' gestation, during labour, and for 1 week after birth given to mother and infant; zidovudine plus lamivudine at labour onset until 1 week after birth given to mother and infant; zidovudine plus lamivudine at onset of labour until delivery given to mother only; and placebo. [27] The RCT found that both zidovudine plus lamivudine from 36 weeks' gestation, during labour, and for 1 week after birth in mother and infant, and zidovudine plus lamivudine at labour onset until 1 week after birth in mother and infant, significantly reduced the outcomes of HIV infection, and HIV infection or infant death, at 4–8 weeks compared with placebo, but found no significant difference at 18 months. It found no significant difference between groups in infant mortality at 4–8 weeks, or in stillbirth. The RCT also found no significant difference between zidovudine plus lamivudine given to the mother only at onset of labour until delivery and placebo in HIV infection, infant mortality, or stillbirth.

Antiretrovirals versus placebo in a non-breastfeeding population:
The systematic review identified three RCTs. [28] [29] [30] The first RCT found that zidovudine given to mothers at 14–34 weeks' gestation and through labour, and to infants for up to 6 weeks, significantly reduced HIV infection at 18 months. [28] However, it found no significant difference between treatments in infant mortality or stillbirth. The second RCT found that zidovudine given to mothers alone from 36 weeks' gestation and in labour significantly reduced HIV infection at 6 months. [29] It found no signficant difference between treatments in stillbirth or infant death. The third RCT found no significant difference between zidovudine given to mothers alone from 38 weeks' gestation and in labour and placebo in HIV infection at 6 months or in stillbirths. [30]

Longer versus shorter regimens using the same antiretrovirals in a breastfeeding population:
The systematic review found one RCT. [31] The RCT found no significant difference between zidovudine given to mothers only from 36 weeks' gestation and through labour and zidovudine given to mothers during labour and to infants for 3 days in HIV infection or infant mortality at 4–8 weeks, 6 months, or 18 months.

Longer versus shorter regimens using the same antiretrovirals in a non-breastfeeding population:
The systematic review identified three RCTs, one of which included both non-breastfeeding and breastfeeding women. [32] [33] [34] The first RCT compared four regimens of zidovudine (long-long, LL: from 28 weeks' gestation, during labour, and for 6 weeks to the infant; long-short, LS: from 28 weeks' gestation and during labour, not to the infant; short-long, SL: from 36 weeks' gestation, during labour, and for 6 weeks to the infant; short-short, SS: from 36 weeks' gestation, during labour, and for 3 days to the infant). [32] The short-short group was discontinued at the first interim analysis. The RCT found no significant difference between long-long and short-long regimens in HIV infection at 6 months, but found significantly less HIV infection with long-short compared with short-long regimens. There was no significant difference in infant mortality between regimens. The second RCT found no significant difference in HIV infection at 4–8 weeks between nevirapine given to mothers at onset of labour compared with nevirapine given to mothers at onset of labour plus nevirapine given to infants within 72 hours. However, it found that nevirapine at onset of labour plus nevirapine given to infants within 72 hours significantly reduced infant mortality at 6 months compared with nevirapine at onset of labour alone. All mothers were given zidovudine from 28 weeks' gestation and through labour, and all infants had zidovudine for one week. [33] The third RCT found no significant difference in HIV infection between a longer regimen on zidovudine (62–92 days before delivery and through labour) compared with a shorter regimen (14–35 days before delivery and through labour). [34] It did not assess infant mortality.

Regimens using different drugs and durations of treatment in a breastfeeding population:
The systematic review identified five RCTs, one published in two papers and one of which included both non-breastfeeding and breastfeeding women, [35] [36] [37] [38] [39] [40] and we found two subsequent RCTs. [24] [23] The first RCT identified by the review, published in two papers, found that HIV infection was significantly less at 3–4 months and at 18 months with nevirapine (to mothers at onset of labour until delivery plus within 72 hours to infant) compared with zidovudine (to mothers at onset of labour until delivery plus for 1 week to infant). [35] [36] It found no significant difference between groups in infant mortality. The second RCT identified by the review found that HIV infection at 4–8 weeks was significantly less with nevirapine plus zidovudine given to infant post partum compared with nevirapine alone given to infant post partum but found no significant difference between groups in infant mortality. [37] The third RCT identified by the review found no significant difference in HIV infection or infant mortality at 4–8 weeks between nevirapine plus zidovudine (given to mothers at onset of labour, nevirapine given to infant within 72 hours, and zidovudine given to infants for 1 week) compared with nevirapine alone (given to mothers at onset of labour and to infants within 72 hours). [38] The fourth RCT found no significant difference in HIV infection or infant mortality at 3–4 months between nevirapine (to infant post partum) and zidovudine (for 6 weeks to infant). [39] The fifth RCT, conducted in both breast and non-breastfeeding women, found no significant difference in HIV infection or infant mortality at 4–8 weeks between zidovudine plus lamivudine (at onset of labour and for 1 week, and to infant for 1 week) compared with nevirapine (at onset of labour and for 1 week, and to infant for 1 week). [40] The first subsequent RCT compared nevirapine versus placebo during labour in mothers and infants receiving zidovudine for 1 month plus single-dose nevirapine. [24] It found no significant difference between nevirapine and placebo during labour in HIV infection or infant mortality at 1 month. Nevirapine resistance was detected in 45% of a random sample of the women who received nevirapine. This RCT used a 2x2 factorial design also comparing formula feeding versus breast feeding plus antiretrovirals; see option on different methods of infant feeding, p 6 ; results published in a separate paper. [41] The second subsequent RCT comparing zidovudine versus placebo in mothers and infants receiving nevirapine found no significant difference between groups in the combined outcome of HIV infection or death at 6 weeks. [23] The RCT was terminated at the first interim analysis, as it was unable to recruit sufficient numbers of participants to detect the pre-specified difference of 5% in the primary outcome.

Regimens using different drugs and durations of treatment in a non-breastfeeding population: The systematic review identified four RCTs, one of which included both non-breastfeeding and breastfeeding women. [42] [40] [43] [44] The first RCT found no significant difference in HIV infection at 4–8 weeks between adding nevirapine to standard antiretroviral treatment (at discretion of the treating physician; nevirapine given at onset of labour and to infant within 72 hours) and standard antiretroviral treatment alone. [42] The second RCT found no significant difference in HIV infection at 4–8 weeks between the "Thai CDC" ziduvodine regimen and the "HIVNET 012" nevirapine regimen. It also found no significant difference between regimens in infant mortality or stillbirths. [43] The third RCT found no significant difference in HIV infection or infant mortality at 6 months between stavudine and zidovudine, between didanosine and zidovudine, or between stavudine plus didanosie and zidovudine. [44] The fourth RCT, conducted in both breast and non-breastfeeding women, found no significant difference in HIV infection at 4–8 weeks between zidovudine plus lamivudine (at onset of labour and for 1 week, and to infant for 1 week) compared with nevirapine (at onset of labour and for 1 week, and to infant for 1 week). [40]

Harms:

The systematic review stated that it "found no evidence that short courses of antiretroviral (ART) treatment compared with placebo or other short course ART regimens increased the incidence of serious or life threatening events in mothers or babies." [22]

Antiretrovirals versus placebo in a non-breastfeeding population:
The systematic review identified one RCT, which found that a mild transient anaemia was seen in mothers and babies exposed to the long-course zidovudine. [28] In the RCT using this regimen the frequency of anaemia (Hb less than 9.0 g/dL) in the first 6 weeks of life was higher in infants receiving zidovudine (44 with zidovudine *v* 24 with placebo; P = 0.001; total number of infants assessed not reported); of these, 4 infants in each group had a Hb less than 7.0 g/dL. The anaemia resolved by 12 weeks of age.

Comment:

Clinical guide: The use of highly active antiretroviral treatment (HAART) during pregnancy, especially if total viral suppression (below 50 copies/mL) is achieved/maintained, provides the most effective protection. Results suggest equivalence of choice between the two most widely used short-course regimens: single-dose nevirapine and short-course zidovudine. The greater efficacy of combination drugs (zidovudine and lamivudine; zidovudine and nevirapine; zidovudine, lamivudine, and nevirapine) has not been established. There is limited data from RCTs, and conflicting results have been reported from breastfeeding populations. The use of short-course combination drugs may offer improved protection against the emergence of drug resistance. The emergence of resistant mutations following the use of antiretroviral regimens in the prevention of vertical transmission is a cause for concern, as this may potentially compromise future treatment of infected mothers and babies, including future efforts to reduce MTCT. Data on drug resistance from RCTs is currently limited to information from subgroups.

OPTION DIFFERENT METHODS OF INFANT FEEDING

HIV infection

Formula feeding compared with breast feeding alone Formula feeding in a setting where clean water and health education are available is more effective than breast feeding alone at reducing the risk of MTCT of HIV infection at 24 months (high-quality evidence).

Formula feeding compared with breast feeding plus antiretrovirals for infants Formula feeding is more effective at 7 months at reducing HIV infection compared with breast feeding plus a short course of zidovudine given to infants (moderate-quality evidence).

Early breast feeding compared with mixed feeding Early breast feeding may be more effective than mixed feeding at reducing the risk of HIV infection at 18 months (low-quality evidence).

Infant mortality

Formula feeding compared with breast feeding alone Formula feeding and breast feeding alone seem to be equally effective at reducing mortality at 24 months, although HIV-1-free survival is higher with formula feeding compared with breast feeding (high-quality evidence).

Formula feeding compared with breast feeding plus antiretrovirals for infants Formula feeding may be less effective at 7 months but not at 18 months at reducing cumulative infant mortality compared with breast feeding plus zidovudine given to infants (low-quality evidence).

Early breast feeding compared with mixed feeding Early breast feeding may be more effective than mixed feeding at reducing mortality at 18 months (low-quality evidence).

Note

We found no direct information assessing the effects of heat, or microbicidal treatment of expressed breast milk on HIV transmission.

For GRADE evaluation of interventions for HIV: mother-to-child transmission, **see table, p 20 .**

Benefits:

Formula feeding versus breast feeding alone:
We found no systematic review but found one RCT and a follow-up of the RCT. [5] [45] The RCT compared the effects on HIV infection rates in babies of formula feeding versus breast feeding. It found that formula feeding significantly reduced the proportion of infants with HIV at 24 months compared with breast feeding (425 HIV-1 seropositive women with access to clean water and health education in Kenya; AR 31/205 [15%] with formula feeding *v* 61/197 [31%] with breast feeding; RR 0.49, 95% CI 0.33 to 0.72; NNT 7, 95% CI 5 to 13). Although infants were breastfed throughout the RCT, the greatest exposure to breast milk occurred during the first 6 months of life. The RCT found no significant difference in mortality between the two groups at 24 months (AR 39/204 [19%] with formula feeding *v* 45/197 [23%] with breast feeding; RR 0.84, 95% CI 0.57 to 1.23). [5] In a follow-up study of this RCT, there was no significant difference in estimated mortality rates at 2 years among infants in the formula-fed compared with breastfed infants (20% *v* 24%; HR 0.8; 95% CI 0.5 to 1.3). [45] Infants in the breastfeeding arm tended to have better nutritional status, especially during the first 6 months of life. However, HIV-1-free survival at 2 years was significantly higher with formula compared with breast feeding (42% *v* 30%, P = 0.02).

Formula feeding versus breast feeding plus antiretrovirals for infants:
We found one open label RCT (1200 women from 4 district hospitals) comparing formula feeding versus breast feeding. [41] The RCT had a 2x2 factorial design, and also compared single-dose nevirapine versus placebo given to women during labour (see option on antiretroviral drugs, p 3 ; results published in a separate paper [24]). At 7 months, the RCT found that HIV infection rates were signficantly lower in formula-fed infants than in breastfed-plus-zidovudine infants (proportion infected: 32/526 [6%] with formula *v* 51/541 [9%] with breast feeding plus zidovudine; P = 0.04). While cumulative infant mortality was higher with formula feeding at 7 months (54/559 [9%] with formula *v* 28/575 [5%] with breast feeding plus zidovudine; P = 0.003), there was no significant difference between groups at 18 months (62/573 [12%] with formula *v* 48/529 [9%] with breast feeding plus zidovudine; P = 0.21). [41]

Early breast feeding versus mixed feeding:
We found no systematic review or RCTs. Two prospective vitamin A studies, one from South Africa [46] and one from Zimbabwe, [47] reported that early breast feeding reduced the risk of postnatal HIV-1 transmission, and increased overall infant survival. The study from Zimbabwe enrolled 14,110 mother–newborn pairs, randomly assigned to a vitamin A treatment group and followed for 2 years. Compared with early breast feeding, early mixed feeding was associated with a 2.5-fold (95% CI 1.3 to 4.8) greater risk of HIV infection or death at 18 months.

Heat or microbicidal treatment of expressed breast milk:
We found no systematic reviews or RCTs. The evidence that various pasteurization methods and microbicidal treatment effectively kill HIV in expressed breast milk is summarised in a non-systematic review. [48]

Harms:

Formula feeding versus breastfeeding alone:
In the Kenyan RCT, [45] [5] a follow-up report examined the impact of breast feeding on postpartum maternal mortality. [49] Mortality in the first 2 years postpartum was higher in the breastfeeding than in the formula group; cumulative probability of death was 10% in the breastfeeding compared with 3.8% in the formula group (P = 0.02). One individual patient-data meta-analysis evaluated results from 4237 HIV-infected women; 162 (4%) died within 18 months after delivery. [50] The risk of death during the 18-month period after delivery did not differ significantly according to whether women had "ever" or "never" breastfed. Mothers with lower CD4 counts were less likely to initiate breast feeding, but the outcome remained similar with or without adjustment for maternal CD4 count. One RCT from Zambia randomly assigned 653 HIV-infected women to either a counselling program that encouraged abrupt cessation of breast feeding at 4 months, or to a program that encouraged prolonged breast feeding. [51] There were similar rates of maternal mortality 12 months after delivery (5% in each group). Analysis assessing actual practice, rather than intention to treat, also demonstrated no increased maternal mortality related to breast feeding.

Formula feeding versus breast feeding plus antiretrovirals for infants:
The RCT found a significant increase in grade 3 or higher laboratory abnormalities associated with zidovudine toxicity when comparing breast feeding plus zidovudine versus formula feeding (25% with breast feeding plus zidovudine *v* 15% with formula; P less than 0.001). [41]

Heat or microbicidal treatment of expressed breast milk:
Heat treatment of expressed breast milk may have potentially negative impacts on the nutritional value and immunologically active components of breast milk.

Comment:

Clinical guide:
In settings with good access to clean water and health education, formula feeding reduces HIV transmission and increases HIV-1-free survival. However, where hygienic practices are not observed, morbidity and mortality in formula-fed infants may be increased. The indirect health advantages that breast feeding has on nutrition, immunity, maternal fertility, and birth spacing are well recognised. An analysis of data from two previous RCTs of short-course ART in Malawi (total of 2000 women) found that the risk of death at 2 years of age for HIV-uninfected children was significantly lower in breastfed compared with non-breastfed infants (adjusted HR 0.34, 95% CI 0.18 to 0.64) and in HIV-infected children (adjusted HR 0.36, 95% CI 0.19 to 0.71). [52] Where mothers with HIV choose to breast feed, exclusive breast feeding with weaning around 4–6 months should be promoted in preference to mixed feeding. Heat or microbicidal treatment of expressed breast milk may offer an alternative to formula feeding in settings where the benefits of breast milk are important, as in the care of premature babies in resource-limited settings.

OPTION ELECTIVE CAESAREAN SECTION

HIV infection
Compared with vaginal delivery Elective caesarean section is more effective than vaginal delivery at reducing HIV transmission to infants at 18 months (moderate-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, see table, p 20 .

Benefits:

We found two systematic reviews (search date not stated [53] and 2004 [54]), which identified the same RCT comparing elective caesarean section at 38 weeks versus vaginal delivery. The RCT found that caesarean section significantly reduced HIV transmission to infants at 18 months compared with vaginal delivery (436 HIV-seropositive women; AR 3/170 [2%] with caesarean section *v* 21/200 [11%] with vaginal delivery; RR 0.16, 95% CI 0.05 to 0.55; NNT 11, 95% CI 10 to 21).

Harms:

Both systematic reviews reported no serious adverse effects associated with either caesarean or vaginal delivery. [53] [54] Postpartum fever was significantly more common in women undergoing caesarean section than in those undergoing vaginal delivery (15/225 [7%] with caesarean section *v* 2/183 [1%] with vaginal delivery; RR 6.1, 95% CI 1.5 to 22.0; NNH 18, 95% CI 16 to 50). Postpartum bleeding, intravascular coagulation, and severe anaemia were rare in both groups. Five observational studies identified by the second systematic review also found a trend toward an increased risk of increased postpartum morbidity (such as haemorrhage, peritonitis, sepsis, thromboembolism, anaemia, and fever) with elective caesarean section compared with vaginal delivery, but the review did not meta-analyse the results of these studies. [54]

Comment:

About 15% of women withdrew from the RCT or were lost to follow-up. [53] None of the women breast fed, although this was not stated as a specific exclusion criterion. More women who gave birth by caesarean section compared with vaginal delivery had received zidovudine during pregnancy (70% with caesarean section *v* 58% with vaginal delivery); this means that the observed difference between groups may not have been exclusively due to the different delivery methods. [53]

Clinical guide: Elective caesarean section may reduce the risk of MTCT in the absence of complete viral suppression. However, in resource-limited settings, the health risks of caesarean section to mothers and babies may be increased owing to a lack of technical expertise and/or the availability of adequate aseptic conditions.

OPTION IMMUNOTHERAPY

HIV infection
HIV hyperimmune globulin compared with immunoglobulin without HIV antibody HIV hyperimmune globulin and immunoglobulin without HIV antibody seem to be equally effective at reducing the risk of transmission of HIV to infants up to 6 months of age from mothers who are also taking zidovudine (high-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, see table, p 20 .

Benefits:

We found one systematic review (search date not reported), which identified one RCT comparing HIV hyperimmune globulin versus immunoglobulin without HIV antibody given to women during pregnancy, the intrapartum period, and to their infants at birth. [53] Women in both groups received

a standard course of zidovudine. The RCT found no significant difference in transmission of HIV up to 6 months of age between HIV hyperimmune globulin and immunoglobulin without HIV antibody regimens (501 HIV-seropositive, non-breastfeeding women; HIV transmission: 4% with HIV hyperimmune globulin *v* 6% with immunoglobulin without HIV antibody; RR 0.67, 95% CI 0.29 to 1.55). [53]

Harms: The RCT found no significant differences between the comparison groups in neonatal haemotological toxicity (1 RCT, 506 infants; RR 1.15, 95% CI 0.65 to 2.07). [53]

Comment: The low overall transmission rate (5%) in this RCT was much lower than the anticipated rate of greater than 15% used to calculate the appropriate sample size. The RCT might have been underpowered to detect a clinically important effect of HIV hyperimmune globulin on the number of children with HIV. [53]

Clinical guide: There is no clinical indication for the use of immunoglobulin to reduce the risk of MTCT of HIV.

OPTION VAGINAL MICROBICIDES

HIV infection

Compared with no vaginal microbicides Vaginal cleansing with microbicides may be no more effective than no vaginal microbicides at reducing the risk of HIV transmission to infants (low-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, see table, p 20 .

Benefits: We found one systematic review (search date 2004), which identified two RCTs comparing vaginal cleansing with microbicides versus no vaginal microbicides. [55] The first RCT compared vaginal cleansing with chlorhexidine (0.2%) versus no cleansing (see comment below, p 9). The second RCT compared daily vaginal cleansing with benzalkonium chloride capsules versus placebo capsules from week 36 of pregnancy until labour (see comment below, p 9). The review found no significant difference in the risk of HIV transmission between vaginal cleansing with microbicides and no vaginal microbicides (2 RCTs, 708 HIV infected women; 74/360 [21%] with vaginal microbicides *v* 76/348 [22%] with no vaginal microbicides; RR 0.94, 95% CI 0.71 to 1.25). [55]

Harms: The review found no significant difference between vaginal cleansing with microbicides and no vaginal microbicides in the risk of maternal adverse events, which included symptoms or signs of mucosal irritation affecting the reproductive tract (1 RCT, 108 women; 46/54 [85%] with vaginal microbicides *v* 45/54 [83%] with no vaginal microbicides; RR 1.02, 95% CI 0.87 to 1.20). [55] It also found no significant difference between vaginal microbicides and no microbicides in neonatal death (RR 1.36, 95% CI 0.32 to 5.79), or death after the neonatal period (RR 1.39, 95% CI 0.52 to 3.71). The review found that vaginal microbicides significantly reduced adverse effects in neonates compared with no microbicides (RR 0.45, 95% CI 0.32 to 0.64). [55]

Comment: The first RCT was quasi-randomised; participating women were allocated to vaginal cleansing with chlorhexidine or no vaginal cleansing in alternate weeks. [55] The second RCT identified by the review was block randomised and was designed and powered to assess the effect on genital ulcers of vaginal cleansing with benzalkonium chloride capsules. The RCT was not powered to investigate the effects on the risk of MTCT of HIV.

Clinical guide: At present, vaginal microbicides cannot be recommended for any clinical application; in particular, there is no evidence of its value to reduce the risk of MTCT of HIV.

OPTION VITAMIN SUPPLEMENTS

HIV infection

Compared with placebo or control Vitamin A supplements taken by HIV-positive women during the antenatal and intrapartum periods is no more effective than placebo or control at reducing the risk of MTCT of HIV infection (moderate-quality evidence). A single megadose of vitamin A given postpartum to either HIV-infected mothers, their infants, or to both is no more effective than placebo or control at reducing the risk of MTCT of HIV infection (moderate-quality evidence).

Multivitamins compared with placebo Multivitamins given to mothers infected with HIV during pregnancy and lactation are no more effective at 6 weeks than placebo at reducing the risk of HIV transmission to infants (high-quality evidence).

Infant mortality

Large single dose of vitamin A compared with placebo or control A single megadose of vitamin A given postpartum to either HIV-infected mothers, their infants, or to both is no more effective than placebo or control at reducing infant mortality at 24 months (high-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, **see table, p 20 .**

Benefits:

Vitamin A:
We found one systematic review (search date 2004), which compared vitamin A supplements (with or without multivitamins) versus placebo or no vitamin A supplements (control) in HIV-infected women during the antenatal and intrapartum periods. [56] The review found no significant difference between vitamin A and control in the risk of HIV transmission from mother to infant (3 RCTs, 2022 women; AR 292/1014 [29%] with vitamin A *v* 265/1008 [26%] with control; RR 1.10, 95% CI 0.95 to 1.26; see comment below, p 9). One subsequent RCT compared the effect of a single large dose of vitamin A given during the postpartum period to either HIV-infected women, their infants, or both groups, on child HIV infection, HIV-free survival, and mortality. [57] A total of 14,110 mother–infant pairs were enrolled up to 96 hours after delivery. Neither maternal nor neonatal vitamin A supplementation significantly affected MTCT. The RCT found no significant difference between vitamin A compared with placebo in HIV infection or mortality at 24 months (HIV infection: HR 1.03, 95% CI 0.87 to 1.22; mortality: HR 1.02, 95% CI 0.84 for 1.25).

Multivitamins:
We found one RCT. [58] It found no significant difference between multivitamins (given to mothers with HIV during pregnancy and lactation) and placebo in HIV transmission to infants at 6 weeks (AR 16% with multivitamins *v* 16% with placebo; RR 1.04, 95% CI 0.65 to 1.66).

Harms:

Vitamin A:
The systematic review found no significant difference between vitamin A supplements and no vitamin A in the risk of stillbirth, preterm birth before 34 or 37 weeks, low birth weight (less than 2500 g), infant death before 24 months, or maternal death (stillbirth: 4 RCTs; AR 53/1441 [3.7%] with vitamin A *v* 53/1414 [3.7%] with no vitamin A; RR 0.99, 95% CI 0.68 to 1.43; preterm birth before 34 weeks: 2 RCTs; AR 44/793 [5.5%] with vitamin A *v* 50/785 [6.4%] with no vitamin A; RR 0.87, 95% CI 0.59 to 1.29; preterm birth before 37 weeks: 3 RCTs; AR 182/1071 [17%] with vitamin A *v* 195/1039 [19%] with no vitamin A; RR 0.91, 95% CI 0.76 to 1.09; low birth weight: 4 RCTs; AR 157/1309 [12%] with vitamin A *v* 189/1297 [15%] with no vitamin A; RR 0.83, 95% CI 0.68 to 1.01; infant death before 24 months: 1 RCT; AR 58/285 [20%] with vitamin A *v* 58/309 [19%] with no vitamin A; RR 1.08, 95% CI 0.78 to 1.50; maternal death: 1 RCT; AR 1/368 [0.3%] with vitamin A *v* 2/360 [0.6%] with no vitamin A; RR 0.49, 95% CI 0.04 to 5.37). [56] The RCT testing postpartum single-dose vitamin A found that the timing of infant HIV infection influenced the effect of vitamin A supplementation on mortality. In breastfed children who were PCR negative at 6 weeks, all three vitamin A regimens doubled the risk of death by 24 months. [57]

Multivitamins:
Long-term follow-up [59] of the RCT [58] found no significant difference between multivitamins and placebo in infant death at 24 months (AR 24% with multivitamins *v* 26% with placebo; RR 0.91, 95% CI 0.71 to 1.17).

Comment:

The RCTs included in the review were performed because observational studies have found an association in pregnant women between transmission of HIV and low serum levels of vitamin A. [60] The review found significant heterogeneity between the included RCTs. [56] Two of the RCTs included in the review found no significant difference at follow-up in the risk of HIV transmission between vitamin A supplementation and no supplementation, whereas the third RCT found that vitamin A supplementation significantly increased the risk of transmission of HIV infection from mother to child. One RCT enrolled 1078 HIV-infected pregnant women in a double-blind placebo controlled trial in Dar es Salaam, Tanzania, comparing the effect of multivitamins on maternal health and HIV disease progression. [58] The RCT found that signficantly fewer women progressed to WHO stage 4 disease with multivitamins compared with placebo (67/271 [25%] v 82/267 [31%]; RR 0.7, 95% CI 0.51 to 0.98). The RCT did not comment on MTCT risk in the various groups.

Clinical guide: Supplementation with vitamin A or multivitamins is not indicated for preventing MTCT of HIV. There is reason for concern that universal maternal and neonatal vitamin A supplementation in HIV-endemic areas may lead to more harm than good.

GLOSSARY

Human immunodeficiency virus type 1 (HIV-1) is the most common cause of HIV disease throughout the world.
Human immunodeficiency virus type 2 (HIV-2) is predominantly found in West Africa and is more closely related to the simian immunodeficiency virus than to HIV-1.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence 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.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antiretroviral drugs One update of a systematic review [22] and one subsequent RCT added. [23] Benefits and harms data expanded and additional outcomes of interest added. Categorisation unchanged (Beneficial).
Different methods of infant feeding One follow-up of one RCT comparing breast feeding alone versus formula feeding added; [45] and one RCT comparing breast feeding plus antiretrovirals given to the infant versus formula feeding added. [41] Categorisation unchanged: avoiding breast feeding categorised as Likely to be beneficial (even in infants receiving antiretrovirals), provided there is access to clean water and to education.
Vitamin supplements One subsequent RCT added; [57] categorisation unchanged (Likely to be ineffective or harmful).

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Disclaimer

TABLE 1 **Summary of randomised controlled trials, by publication date, that evaluated the effects of antiretroviral drugs to reduce mother-to-child transmission of HIV-1 (see text).**

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative Risk Reduction (RRR)/efficacy (95% CI)	Infant mortality Relative Risk (RR) (95% CI)	Still birth Relative Risk (RR) (95% CI)
PACTG 076; NEJM 1994 [28]	USA & France 60 centres 409 women	ZDV *v* placebo in mothers and infants No breast feeding Mother ZDV antepartum orally 100 mg 5 times daily starting at 14–34 weeks' gestation ZDV intrapartum iv 2 mg/kg over 1 hour then 1 mg/kg/h until delivery Infant ZDV orally 2 mg/kg every 6 hours for 6 weeks	At 18 months ZDV 8.3% Placebo 25.5% **RRR** 66% (35–97)	At 18 months **RR** 1.33 (0.30–5.87)	At 18 months **RR** 0.33 (0.01–8.11)
Thai-CDC; Lancet 1999 [29]	Thailand 2 hospitals 393 women	ZDV *v* placebo in mothers No breast feeding Mother ZDV antepartum orally 300 mg twice daily from 36 weeks' gestation ZDV intrapartum orally 300 mg every 3 hours until delivery Infant No ART	At 6 months ZDV 9% Placebo 19% **RRR** 50% (15–70)	In the first 4–8 weeks of life **RR** 0.50 (0.05–5.50)	**RR** 3.02 (0.12–73.57)
DITRAME Study 1; Lancet 1999; [25]	Ivory Coast 1 clinic 280 women	ZDV *v* placebo in mothers Breast feeding Mother ZDV antepartum orally 300 mg twice daily from 36 weeks' gestation ZDV intrapartum orally 300 mg every 3 hours until delivery Infant No ART	At 4–8 weeks ZDV 12.2% Placebo 21.7% **RRR/efficacy** 44% (9–79) At 3–4 months ZDV 15.7% Placebo 24.9% **RRR** 37% (4–70)	In the first week of life **RR** 0.13 (0.02–0.99) In the first 3 to 4 months of life **RR** 0.15 (0.05–0.49)	**RR** 3.50 (0.74–16.55)

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative Risk Reduction (RRR)/efficacy (95% CI)	Infant mortality Relative Risk (RR) (95% CI)	Still birth Relative Risk (RR) (95% CI)
DITRAME Study 2 Lancet 1999 [26]	Ivory Coast & Burkina Faso Multiple clinics 421 women	ZDV *v* placebo in mothers Breast feeding Mother ZDV antepartum orally 300 mg twice daily from 36–38 weeks' gestation ZDV intrapartum orally single dose 600 mg at onset of labour ZDV postpartum orally 300 mg twice daily for 7 days Infant No ART	At 3–4 months **RRR** 34.00 (6.56–61.44) At 6 months **RRR** 35% (10–60) At 12 months **RRR** 34 (9–60) At 18 months **RRR** 30 (3–57)	In the first week of life **RR** 2.03 (0.51–8.0) In the first 4–8 weeks **RR** 1.77 (0.53–5.97) In the first 3–4 months **RR** 0.74 (0.3–1.58) In the first 6 months **RR** 0.62 (0.35–1.09) In the first 12 months **RR** 0.75 (0.48–1.17) In the first 18 months **RR** 0.80 (0.53–1.21)	**RR** 0.14 (0.02–1.17)
HIVNET 012 Lancet 1999 (6-month follow-up) [35] Lancet 2003 (18-month follow-up) [36]	Uganda 1 hospital 626 women	NVP *v* ZDV in mothers and infants Breast feeding NVP Mother NVP orally 200 mg at onset of labour Infant NVP orally 2 mg/kg within 72 hours of delivery ZDV Mother ZDV orally 600 mg at onset of labour; 300 mg every 3 hours until delivery Infant ZDV orally 4 mg/kg twice daily for 1 week	At 4-8 weeks ZDV 21.3% NVP 11.9% At 3–4 months ZDV 25.1% NVP 13.1% **RRR** 39% (12–66) At 18 months ZDV 25.8% NVP 13.5% **RRR** 39% (14–64)	In the first week of life **RR** 2.50 (0.49–12.79) At 4–8 weeks **RR** 2.50 (0.79–7.89) At 18 months **RR** 1.24 (0.81–1.89)	**RR** 2.00 (0.18–21.94)

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative Risk Reduction (RRR)/efficacy (95% CI)	Infant mortality Relative Risk (RR) (95% CI)	Still birth Relative Risk (RR) (95% CI)
PHPT-1; N Engl J Med 2000; [32]	Thailand 27 sites 1437 women	Various durations of ZDV *v* each other in mothers and infants No breast feeding Mother *ZDV long-long (LL)* ZDV antepartum orally 300 mg twice daily starting at 28 weeks' gestation ZDV intrapartum orally 300 mg every 3 hours until delivery Infant ZDV orally 2 mg/kg every 6 hours for 6 weeks *ZDV long-short (LS)* Mother ZDV from 28 weeks antepartum Infant No ZDV *ZDV short-long (SL)* Mother ZDV from 36 weeks antepartum Infant ZDV for 6 weeks *ZDV short-short (SS)* Mother ZDV from 36 weeks antepartum Infant ZDV for 3 days to infant	At 6 months LL 6.5% LS 4.7% SL 8.6% SS 10.5% **RRR** LL *v* SL +24% (–21 to +69) **RRR** LS *v* SL 45% (2–88) SS discontinued at first interim analysis	LL *v* SL At 6 months **RR** 0.82 (0.24 –2.82) LS *v* SL At 6 months **RR** 1.38 (0.44–4.31)	LL *v* SL **RR** 0.55 (0.23–1.33) LS *v* SL **RR** 0.33 (0.11–1.01)
Limpongsanurak J Med Assoc Thai 2001 [30]	Thailand 3 hospitals 182 women	ZDV *v* placebo in mothers No breast feeding Mother ZDV ZDV 250 mg orally twice daily from 38 weeks anetpartum ZDV iv 2 mg/kg during first hour of labour, then 1 mg/kg until delivery Infant No treatment Placebo Mother Placebo capsules and 5% iv dextrose during labour Infant No treatment	At 6 months ZDV 14.9% Placebo 16.3% **RRR** +9% (–26 to +44)	NR	**RR** 3.07 (0.13–74.28)

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative Risk Reduction (RRR)/efficacy (95% CI)	Infant mortality Relative Risk (RR) (95% CI)	Still birth Relative Risk (RR) (95% CI)
PETRA A, B, & C Lancet 2002 [27]	South Africa, Uganda, Tanzania 5 sites 1797 women	ZDV + 3TC *v* placebo in mothers and infants Breast feeding and no breast feeding Petra A Mother ZDV antepartum orally 300 mg + 3TC 150 mg twice daily from 36 weeks' gestation ZDV intrapartum orally 300 mg every 3 hours until delivery + 3TC 150 mg twice daily ZDV 300 mg + 3TC 150 mg orally twice daily postpartum for 1 week Infant ZDV 4 mg/kg + 3TC 2 mg/kg orally twice daily for 1 week Petra B Mother ZDV 600 mg orally intrapartum at onset of labour, then 300 mg every 3 hours + 3TC 150 mg twice daily until delivery ZDV 300 mg + 3TC 150 mg twice daily post partum for 1 week Infant ZDV 4 mg/kg + 3TC 2 mg/kg orally twice daily for 1 week Petra C Mother ZDV 600 mg orally intrapartum at onset of labour then 300 mg every 3 hours until delivery Infant No treatment	At 4–8 weeks Petra A 7.0% Petra B 11.6% Petra C 17.5% Placebo 18.1% **RRR Petra A *v* placebo** 63% (41–85) **RRR Petra B *v* placebo** 42% (13–71) **RRR Petra C *v* placebo** +7% (–32 to +46) At 18 months **RRR Petra A *v* placebo** 33 (–12 to +78; absolute numbers not reported) **RRR Petra B *v* placebo** 18% (–27 to +63)**RRR Petra C *v* placebo** 10% (–41 to +61) With prolonged breast feeding, transmission rates for all groups combined were 80%	In the first 4–8 weeks Petra A *v* placebo **RR** 0.35 (0.11–1.14) Petra B *v* placebo **RR** 0.71 (0.28–1.81) Petra C *v* placebo RR 0.98 (0.41–2.34) In the first 18 months Petra A *v* placebo RR 0.76 (0.50–1.14) Petra B *v* placebo RR 1.05 (0.73–1.51) Petra C *v* placebo RR 0.96 (0.66–1.39)	Petra A *v* placebo **RR** 0.40 (0.07–2.15) Petra B *v* placebo **RR** 1.19 (0.34–4.20) Petra C *v* placebo **RR** 0.80 (0.20–3.18)
PACTG 316; JAMA 2002 [42]	United States, Europe, Brazil, Bahamas Multiple sites 1270 women	NVP *v* placebo in mothers receiving standard ART at discretion of treating physician and NVP in infants No breast feeding Mother NVP 200 mg orally intrapartum at onset of labour Infant NVP 2 mg/kg orally within 72 hours	At 4–8 weeks Standard ART 1.6% ART+NVP 1.4% **RRR** 13% (–83 to +109) Study stopped early	At 4–8 weeks **RR** 0.60 (0.14–2.50)	**RR** 2.99 (0.12–73.33)
SAINT; J Infect Dis 2003 [40]	South Africa 11 sites 1317 women	ZDV + 3TC *v* NVP in mothers and infants Breast feeding and no breast feeding (approximately 45% breast fed at delivery; 30% at 8 weeks) ZDV Mother ZDV 600 mg orally intrapartum at onset of labour, then 300 mg every 3 hours + 3TC 150 mg twice daily until delivery ZDV 300 mg + 3TC 150 mg twice daily post partum for 1 week Infant ZDV 4 mg/kg + 3TC 2 mg/kg orally twice daily for 1 week NVP Mother NVP 200 mg orally intrapartum at onset of labour Infant NVP 6 mg orally within 48 hrs	At 4–8 weeks NVP 12.3% ZDV+ 3TC 9.3% **RRR** 24% (–5 to +53) Increased HIV transmission risk in breastfeeding group **Odds ratio (OR)** 7 (2–25)	At 4 to 8 weeks RR 1.01 (0.54–1.89)	NR

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative Risk Reduction (RRR)/efficacy (95% CI)	Infant mortality Relative Risk (RR) (95% CI)	Still birth Relative Risk (RR) (95% CI)
Kiarie 2003; AIDS 2003 [43]	Kenya 1 hospital 188 women	THAI CDC ZDV regimen in mothers *v* HIVNET 012 NVP regimen in mothers and infants No breast feeding	At 4–8 weeks THAI CDC ZVD 9% HIVNET 012 NVP 22% **RRR** 58% (–5–120)	At 4–8 weeks **RR** 0.99 (0.21–4.72)	**RR** 1.48 (0.25–8.58)
NVAZ; Lancet 2003 [37]	Malawi 6 clinics 1119 women	NVP *v* NVP + ZDV in infants Breast feeding Infant NVP 2 mg/kg stat oral dose postpartum NVP + ZDV NVP as above + ZDV 4 mg/kg twice daily for 1 week	At 4–8 weeks NVP 20.9% NVP + ZDV 15.3% **RRR** 37% (4–70)	At 4–8 weeks **RR** 1.26 (0.60–2.67)	NR
Thistle 2004; Centr Afr J Med 2004 [31]	Zimbabwe 1 hospital 222 women	Different regimens of ZDV *v* each other Breast feeding Mother ZDV antepartum 300 mg twice daily from 36 weeks' gestation ZDV intrapartum 300 mg every 3 hours during labour Infant Placebo Mother Placebo antepartum 300 mg twice daily from 36 weeks' gestation ZDV intrapartum 300 mg every 3 hours during labour Infant ZDV 2mg/kg twice daily for 3 days	At 4–8 weeks ZDV 18.9% Placebo 15.7% **RRR** 17% (–42 to 76) At 6 months 8% (43 to +59) At 18 months 9% (–34 to +52)	At 4–8 weeks ZDV *v* placebo **RR** 1.00 (0.21–4.85) At 3–4 months **RR** 1.75 (0.53–5.81) At 6 months **RR** 2.00 (0.71–5.66) At 12 months **RR** 2.00 (0.71–5.66)	None in either group
Taha 2004; JAMA 2004 [38]	Malawi 6 clinics 894 women	ZDV + NVP *v* NVP alone in infants Breast feeding Mother NVP 200 mg at onset of labour to all mothers Infant ZDV + NVP ZDV 4 mg/kg orally twice daily for 1 week + NVP 2 mg/kg within 72 hours of delivery NVP alone NVP 2 mg/kg within 72 hours of delivery	At 4–8 weeks NVP 14.1% NVP + ZDV 16.3% **RRR** 13% (–16 to +42)	**RR** 1.74 (0.51–5.91)	NR

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative Risk Reduction (RRR)/efficacy (95% CI)	Infant mortality Relative Risk (RR) (95% CI)	Still birth Relative Risk (RR) (95% CI)
PHPT-2; N Engl J Med 2004 [33]	Thailand 37 sites 1844 women	NVP *v* placebo in 4 different regimens to mothers and infants No breast feeding All mothers received oral ZDV 300 mg twice daily from 28 weeks' gestation and 300 mg every 3 hours once in labour All infants received oral ZDV 2 mg/kg every 6 hours for 1 week *NVP-PL* Mother NVP 200 mg orally at onset of labour Infant placebo NVP-NVP Mother NVP 200 mg orally at onset of labour Infant NVP 6 mg orally within 72 hours of birth PL-PL Mother placebo Infant placebo	At 6 months NVP-PL 2.8% NVP-NVP 1.9% Placebo-Placebo 6.5% **RRR** NVP-NVP *v* NVP-PL 29% (–26 to +84) Placebo arm discontinued at first interim analysis	At 6 months NVP-NVP *v* NVP-PL **RR** 0.20 (0.04–0.91)	NVP-NVP *v* NVP-PL **RR** 0.25 (0.05–1.17) Placebo-Placebo arm discontinued at first interim analysis
Gray 2005 AIDS 2005 [39]	South Africa 3 hospitals 1530 women	NVP *v* ZDV in infants Breast feeding Infant NVP 2 mg/kg orally postpartum ZDV 4 mg/kg orally twice daily for first 6 weeks	At 3–4 months NVP 7.9% ZDV 13.1% **RRR** 40% (–1 to +81) This analysis excluded infants already infected at birth	At 4–8 weeks **RR** 1.15 (0.52–2.54)	NR
Bhoopat 2005 J Acquir Immune Defic Syndr 2005 [34]	Thailand 2 hospitals 50 women	Different regimens of ZDV *v* each other No breast feeding Long Mother ZDV antepartum orally 300 mg twice daily from 62–92 days prior to delivery ZDV intrapartum 300 mg orally every 3 hours until delivery Infant No treatment Short Mother ZDV as above but only from 14–35 days prior to delivery Infant No treatment	At 3–4 months ZDV long 0% ZDV short 14.8% **RRR** 100% (–294 to +494)	NR	NR

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative Risk Reduction (RRR)/efficacy (95% CI)	Infant mortality Relative Risk (RR) (95% CI)	Still birth Relative Risk (RR) (95% CI)
Gray 2006; J Acquir Immune Defic Syndr 2006 [44]	South Africa 1 hospital 373 women	d4T alone *v* ddI alone *v* d4T + ddI *v* ZDV (4 arms) No breast feeding Mother d4T alone d4T 40 mg orally twice daily ante- and intrapartum (from 34–36 weeks' gestation). An additional dose was administered approx 1 hour before delivery ddI alone ddI 200 mg orally twice daily ZDV ZDV 300 mg twice daily Infant Same regimen as the mother continued for 6 weeks postpartum	At 6 months d4T 12.1% ddI 10.6% d4T + ddI 4.6% ZDV 5.6% **d4T *v* ZDV** **RR R** 116% (–280 to +49) **d4T plus ddI *v* ZDV** RRR 89% (–248 to +70)	**d4T *v* ZDV** At 6 months **RR** 2.97 (0.83–10.61) d4T plus ddI *v* ZDV **RR** 0.66 (0.11–3.86)	NR
Mashi Report 1; AIDS 2006; [24]	Botswana 4 sites Report 1 709 women	NVP *v* placebo during labour Breast feeding Mother NVP 300 mg 3-hourly during labour All mothers ZDV 300 mg orally twice daily from 36 weeks' gestation + ZDV 300 mg during labour All infants ZDV 4 mg/kg twice daily orally for 4 weeks + NVP single dose.	At 4 weeks 15/345 [4.3%] with NVP *v* 13/353 [3.7%] with PL **ARR** –0.6% (–2.4% to +3.8%)	At 4 weeks 7/345 [2%] with NVP *v* 13/353 [4%] with PL P = 0.26	
Thistle 2007; Pediatrics 2007 [23]	Zimbabwe 1 hospital 609 infants	ZDV *v* placebo in mothers and infants receiving nevirapine Breast feeding Mother ZDV antepartum 300 mg twice daily from 36 weeks gestation ZDV intrapartum 300 mg every 3 hours Infant ZDV 2 mg/kg orally every 6 hours for 3 days All mothers nevirapine 200 mg and infants 2 mg/kg within 72 hours of delivery	HIV infection or death at 6 weeks NVP 23.6% ZDV+ NVP 21.8% **ARR** 1.8% (–5 to +8) Study discontinued at first interim analysis because could not recruit sufficient numbers of participants to demonstrate the pre-specified difference of 5% in the primary outcome	Reported only as a combined outcome; see HIV infection	NR

iv = intravenously; Ref = reference; ZDV = zidovudine; NVP = nevirapine; 3TC = lamivudine; d4T = stavudine; ddI = didanosie; ART = anti-retroviral therapy; NS = not significant. *efficacy as reported in the Cochrane review

TABLE GRADE evaluation of interventions for HIV: mother-to-child transmission

Important outcomes	HIV infection status of child, morbidity, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of measures to reduce mother-to-child transmission of HIV?									
3 (2498) [25] [26] [27]	HIV infection	Antiretrovirals *v* placebo in a breastfeeding population	4	0	–1	–1	0	Low	Consistency point deducted for different results at different endpoints. Directness point deducted for inclusion of non-breastfeeding women in one RCT
3 (2498) [24] [25] [26]	Infant mortality	Antiretrovirals *v* placebo in a breastfeeding population	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of non-breastfeeding women in one RCT
3 (984) [28] [29] [30]	HIV infection	Antiretrovirals *v* placebo in a non-breastfeeding population	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of breastfeeding women in one RCT
2 (984) [27] [28] [29]	Infant mortality	Antiretrovirals *v* placebo in a non-breastfeeding population	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of breastfeeding women in one RCT
1 (222) [31]	HIV infection	Longer *v* shorter regimens using the same antiretrovirals in a breastfeeding population	4	0	0	0	0	High	
1 (222) [31]	Infant mortality	Longer *v* shorter regimens using the same antiretrovirals in a breastfeeding population	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (3331) [32] [33] [34]	HIV infection	Longer *v* shorter regimens using the same antiretrovirals in a non-breastfeeding population	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
2 (3281) [32] [33] [34]	Infant mortality	Longer *v* shorter regimens using the same antiretrovirals in a non-breastfeeding population	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
6 (6195) [24] [35] [36] [37] [38] [39] [40]	HIV infection	Regimens using different drugs and durations of treatment in a breastfeeding population	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for inclusion of breastfeeding women in one RCT
6 (6195) [24] [35] [36] [37] [38] [39]	Infant mortality	Regimens using different drugs and durations of treatment in a breastfeeding population	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of breastfeeding women in one RCT
4 (3148) [40] [44] [42] [43]	HIV infection	Regimens using different drugs and durations of treatment in a non-breastfeeding population compared with each other	4	–1	0	–1	0	Low	Quality point deducted for short follow-up in one study. Directness point deducted for inclusion of breastfeeding women in one RCT
4 (3148) [40] [44] [42] [43]	Infant mortality	Regimens using different drugs and durations of treatment in a non-breastfeeding population compared with each other	4	–2	0	–1	0	Very low	Quality point deducted for short follow-up in one study and incomplete reporting of results. Directness point deducted for inclusion of breastfeeding women in one RCT
1 (425) [5] [45]	HIV infection	Formula feeding *v* breastfeeding alone	4	0	0	0	0	High	
1 (425) [5] [45]	Infant mortality	Formula feeding *v* breastfeeding alone	4	0	0	0	0	High	

Important outcomes	**HIV infection status of child, morbidity, mortality, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (1200) [41]	HIV infection	Formula feeding *v* breastfeeding plus antiretrovirals for infants	4	–1	0	0	0	Moderate	Quality point deducted for open label RCT
1 (1200) [41]	Infant mortality	Formula feeding *v* breastfeeding plus antiretrovirals for infants	4	–1	–1	0	0	Low	Quality point deducted for open label RCT. Consistency point deducted for different results at different endpoints
1 study (14110) [47]	HIV infection	Early breastfeeding *v* mixed feeding	2	0	0	0	0	Low	
1 study (14110) [47]	Infant mortality	Earlyn breastfeeding *v* mixed feeding	2	0	0	0	0	Low	
1 (436)	HIV infection	Elective caesarean section *v* vaginal delivery	4	0	0	–1	0	Moderate	Directness point deducted for differences in interventions between groups
1 (501) [53]	HIV infection	HIV hyperimmune globulin *v* immunoglobulin without HIV antibody	4	0	0	0	0	High	
2 (708) [55]	HIV infection	Vaginal microbicides *v* no microbicides	4	–2	0	0	0	Low	Quality points deducted for randomisation flaws and for one RCT set up for investigating different outcome
4 (16132) [56] [57]	HIV infection	Vitamin A supplements *v* placebo/control	4	0	–1	0	0	Moderate	Consistency point deducted for heterogeneity between studies
1 (1078) [58]	HIV infection	Multivitamins *v* placebo	4	0	0	0	0	High	
1 (14110) [57]	Infant mortality	Large single dose of vitamin A supplements *v* placebo/control	4	0	0	0	0	High	

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies
Directness: generaliseability of population or outcomes
Effect size: based on relative risk or odds ratio