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HIV: prevention of 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 antiretroviral treatment, the risk of HIV transmission from infected mothers to their children is 15% to 30% during gestation or labour, with an additional transmission risk of 10% to 20% associated with prolonged breastfeeding. 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, advanced disease, or both, in the presence of other sexually transmitted diseases, and with increased exposure to maternal blood. Mixed feeding practices (breast milk plus other liquids or solids) and prolonged breastfeeding are also associated with increased risk of mother-to-child transmission of HIV. 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 October 2009 (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 53 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, micronutrient supplements, vaginal microbicides, and vitamin supplements.

QUESTIONS

INTERVENTIONS

REDUCING TRANSMISSION OF HIV

Beneficial

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Unlikely to be beneficial

Likely to be ineffective or harmful

Key points

- Without active intervention, the risk of mother-to-child transmission (MTCT) of HIV-1 is high, especially in populations where prolonged breastfeeding is the norm.
  - Without antiviral treatment, the risk of transmission of HIV from infected mothers to their children is approximately 15% to 30% during pregnancy and labour, with an additional transmission risk of 10% to 20% associated with prolonged breastfeeding.
  - HIV-2 is rarely transmitted from mother to child.
  - Transmission is more likely in mothers with high viral loads, advanced HIV disease, or both.
  - Without antiretroviral treatment (ART), 15% to 35% 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 complications associated with life-long treatment, including adverse effects of antiretroviral drugs, difficulties of adherence across the developmental trajectory of childhood and adolescence, and the development of resistance.
  - From a paediatric perspective, successful prevention of MTCT and HIV-free survival for infants remain the most important focus.
- Antiretroviral drugs given to the mother during pregnancy or labour, to the baby immediately after birth, or to the mother and baby reduce the risk of intrauterine and intrapartum MTCT of HIV-1 and when given to the infant after birth and to the mother or infant during breastfeeding reduce the risk of postpartum MTCT of HIV-1.
- Reductions in MTCT are possible using multidrug 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% to 2%.

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

The development of viral resistance in mothers and infants after single-dose nevirapine and other short-course regimens that include single-dose nevirapine is of concern. An additional short-course of antiretrovirals with a different regimen during labour and early postpartum, and the use of HAART, may decrease the risk of viral resistance in mothers, and in infants who become HIV-infected despite prophylaxis.

World Health Organization guidelines recommend starting prophylaxis with antiretroviral drugs from as early as 14 weeks' gestation, or as soon as possible if women present late in pregnancy, in labour, or at delivery.

- 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 seems no more effective than immunoglobulin without HIV antibody at reducing HIV-1 MTCT risk.
- Vaginal microbicides have not been demonstrated to reduce HIV-1 MTCT risk.
- There is no evidence that supplementation with vitamin A reduces the risk of HIV-1 MTCT, and there is concern that postnatal vitamin A supplementation for mother and infant may be associated with increased risk of mortality.
- We don't know whether micronutrients are effective in prevention of MTCT of HIV as we found no RCT evidence on this outcome.
- Avoidance of breastfeeding prevents postpartum transmission of HIV, but formula feeding requires access to clean water and health education.

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

  Exclusive breastfeeding during the first 6 months may reduce the risk of HIV transmission compared with mixed feeding, while retaining most of its associated benefits.

  In a population where prolonged breastfeeding is usual, early, abrupt weaning may not reduce MTCT or HIV-free survival at 2 years compared with prolonged breastfeeding, and may be associated with a higher rate of infant mortality for those infants diagnosed as HIV-infected at <4 months of age.

  Antiretrovirals given to the mother or the infant during breastfeeding can reduce the risk of HIV transmission in the postpartum period.

  World Health Organization guidelines recommend that HIV-positive mothers should exclusively breastfeed for the first 6 months, after which time appropriate complementary foods can be introduced. Breastfeeding should be continued for the first 12 months of the infant's life, and stopped only when an adequate diet without breast milk can be provided.

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

Clinical context

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 breastfeeding. 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 antiretroviral treatment (ART) to be 15% to 20% in Europe, 15% to 30% in the USA, and 25% to 35% in Africa. [4] The risk of transmission is estimated to be 15% to 30% during pregnancy, with an additional transmission risk of 10% to 20% associated with prolonged breastfeeding. [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 1000 new HIV infections are transmitted daily from

mothers to infants. [6] Of these, more than 80% are in sub-Saharan Africa, where almost 400,000 children were newly infected with HIV in 2008 alone. [6]

AETIOLOGY/ RISK FACTORS

Transmission of HIV to infants is more likely if the mother has a high viral load. [1] [7] [8] Based on polymerase chain reaction (PCR) results of infants at 6 weeks of age, a Tanzanian study reported that a maternal viral load of 50,000 copies/mL or more at delivery was associated with a 4-fold increase in the risk of early transmission (OR 4.21, 95% CI 1.59 to 11.13; P = 0.004). [9] Other maternal risk factors include low CD4+ count, advanced HIV disease, sexually transmitted diseases, chorioamnionitis, prolonged rupture of membranes, vaginal mode of delivery, and obstetric events with bleeding (episiotomy, perineal laceration, and intrapartum haemorrhage). [6] [10] [11] [12] [13] [14] Estimations of the timing of MTCT of HIV-1 during pregnancy indicate that the probability of transmission in non-breastfeeding populations (80%) is highest during late pregnancy (3% at <14 weeks, 3% at 14–28 weeks, 14% at 28–36 weeks, 50% at 36 weeks to labour, and 30% during labour). [15] Prolonged breastfeeding poses a significant additional risk for MTCT, with about 60% of total transmissions occurring during pregnancy, and 40% via breast milk in breastfeeding populations. [15] With the use of effective drug regimens to reduce pre-partum and intrapartum MTCT of HIV, prolonged breast or mixed feeding without continued antiretroviral prophylaxis or treatment becomes the predominant route of transmission. [15] Observational studies have found that mixed feeding (breast milk in combination with other liquids or solids) is associated with a significantly higher risk of postnatal transmission compared with exclusive breastfeeding; prospective cohort studies have reported early mixed feeding (during the infants' first 6 months) to be associated with increased risk of postnatal MTCT of 4.03 (95% CI 0.98 to 16.61; 2060 infants in Zimbabwe who were HIV-negative at 6 weeks) [16] and 6.30 (95% CI 1.1 to 36.4; 622 infants from Cote d'Ivoire who were HIV-negative at or after 30 days). [17] One study also found that prolonged exclusive breastfeeding (beyond 6 months) was associated with an increased risk of postnatal MTCT compared with formula feeding (622 infants from Cote d'Ivoire who were HIV-negative at or after 30 days; increase in risk of MTCT of 7.5, 95% CI 2.0 to 28.2; P = 0.003). [17] Late postnatal transmission (beyond 6 months) contributes substantially to overall MTCT, with prolonged breastfeeding (beyond 6 months) [17] and maternal disease progression (as measured by CD4+ count) identified as risk factors. [18] Data from a small retrospective case series in China (104 women who acquired HIV-1 through postnatal blood transfusion) showed a potential increased risk of MTCT when mothers seroconverted during breastfeeding after becoming infected with HIV-1 through postnatal blood transfusion (MTCT risk 35.8%, 95% CI 26.7% to 44.9%). [19] Data from a meta-analysis of individual patient data found a 2-fold increase in the risk of postnatal transmission among women with CD4+ counts of less than 200 cells/mm^3. [18]

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] One 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] [20] In one prospective cohort study carried out in France, 2% of perinatally infected children (data reported for 348 HIV-1-infected children) displayed no immunological or clinical symptoms by the age of 10 years. [21] The study found that the mother's clinical status during pregnancy, prematurity of the infant, and the child's initial CD4+ and CD8+ counts were associated with disease progression. However, the prognosis of African children with vertically acquired HIV infection seems significantly worse. One meta-analysis of individual patient data for children born to HIV-infected mothers in Africa (3468 children in analysis) estimated that, of the 707 HIV-infected children, 35.2% would have died by 1 year of age, and 52.5% by 2 years of age. By comparison, the study estimated that 4.9% of uninfected children would have died by 1 year of age and 7.6% by 2 years of age. [22] Stage of disease was a significant predictor of mortality; a prospective cohort study (213 infants with HIV) from Zambia found that infants infected with HIV in the intrauterine (0–3 days postpartum) or intrapartum/early postpartum (4–40 days) periods had a significantly higher risk of mortality at 12 months compared with children with late postpartum infection (>40 days) (HR for late postpartum infection *v* intrauterine infection 0.27, 95% CI 0.15 to 0.50; for intrapartum/early postpartum *v* late postpartum infection; P = 0.006). [23] On a population level, HIV accounts for 4% of overall child deaths in sub-Saharan Africa, and each year causes 210,000 child deaths across the continent. [24] Five countries (Botswana, Namibia, Swaziland, Zambia, and Zimbabwe) reported HIV-attributable mortality in excess of 30/1000 in children under the age of 5 years. [25]

AIMS OF INTERVENTION

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

OUTCOMES

HIV infection status of the child; infant HIV-free survival at 2 years; infant morbidity and mortality; adverse effects in mothers, infants, or both.

METHODS

Clinical Evidence search and appraisal October 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to October 2009, Embase 1980 to October 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, including open studies and any number of individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. For the option of antiretroviral treatments for the prevention of intrauterine and intrapartum transmission, we have included RCTs in which treatment was given to the mother during gestation or labour; some RCTs include treatment for the infant. For the option of antiretroviral treatments for the prevention of postpartum transmission, we have included RCTs here that carried out an analysis of infants who were diagnosed as HIV negative at birth. 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. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 31). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

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

OPTION ANTIRETROVIRAL DRUGS TO PREVENT INTRAUTERINE AND INTRAPARTUM TRANSMISSION OF HIV

HIV transmission

Antiretrovirals compared with placebo (breastfeeding population) Antiretrovirals (various regimens) given to the mother during gestation and during labour and to the infant during the perinatal period are more effective at reducing intrauterine and intrapartum mother-to-child transmission (MTCT) of HIV infection in infants born to women who breastfeed (moderate-quality evidence).

Different durations of regimens using the same antiretrovirals compared with each other (breastfeeding population) In women who breastfeed, zidovudine given to only mothers from 36 weeks and zidovudine given to both mothers during labour and to infants for 3 days are equally effective at reducing the risk of HIV infection in infants at 4 weeks to 18 months (high-quality evidence).

Different antiretroviral regimens compared with each other (breastfeeding population) We don't know how different antiretroviral regimens compare with each other at reducing the risk of MTCT HIV infection in infants at 4 weeks to 18 months born to women who breastfeed; RCTs comparing different drug regimens have mostly found no significant difference between regimens (low-quality evidence).

Antiretrovirals compared with placebo (non-breastfeeding population) 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 at reducing intrauterine and intrapartum MTCT of HIV infection in infants born to women who do not breastfeed (high-quality evidence).

Different durations of regimens using the same antiretrovirals compared with each other (non-breastfeeding population) Zidovudine from 28 weeks' gestation with 3 days of zidovudine for the infant is more effective than zidovudine from 36 weeks' gestation with 6 weeks of zidovudine for the infant and as effective as zidovudine from 36 weeks' gestation with 6 weeks of zidovudine for the infant at reducing HIV transmission in infants born to mothers who do not breastfeed (moderate-quality evidence).

Different antiretroviral regimens compared with each other (non-breastfeeding population) Different antiretroviral regimens (various) seem to be as effective as each other at reducing the risk of MTCT HIV infection in infants at 4

weeks to 18 months born to women who do not breastfeed; RCTs comparing different drug regimens have mostly found no significant difference between regimens (moderate-quality evidence).

Infant mortality

Antiretrovirals compared with placebo (breastfeeding population) Antiretrovirals (various regimens) given to the mother during gestation and during labour and to the infant during the perinatal period may be no more effective than placebo at reducing infant mortality at 18 months in women who breastfeed (low-quality evidence).

Different durations of regimens using the same antiretrovirals compared with each other (breastfeeding population) In breastfeeding women, longer regimens of zidovudine given to only mothers (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 are equally effective at reducing infant mortality at 4 weeks to 12 months (high-quality evidence).

Different antiretroviral regimens compared with each other (breastfeeding population) Different regimens of antiretrovirals (including zidovudine and nevirapine either alone or in combination with each other) seem equally effective at reducing infant mortality at 4 weeks to 18 months in infants born to women who breastfeed (moderate-quality evidence).

Antiretrovirals compared with placebo (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 seems no more effective than placebo at reducing infant mortality at 6 to 18 months in infants born to women who do not breastfeed; rates of infant mortality are lower with antiretroviral treatment but the differences between groups are not significant (moderate-quality evidence).

Different durations of regimens using the same antiretrovirals compared with each other (non-breastfeeding population) In non-breastfeeding women, zidovudine from 28 weeks' gestation with either 6 weeks of zidovudine to the infant or 3 days of zidovudine to the infant seem as effective as zidovudine from 36 weeks' gestation with 3 days of zidovudine to the infant at reducing infant mortality at 6 months (moderate-quality evidence).

Different antiretroviral regimens compared with each other (non-breastfeeding population) Different regimens of antiretrovirals (including zidovudine and nevirapine either alone or in combination with each other) seem equally effective at reducing infant mortality at 4 weeks to 6 months in infants born to women who do not breastfeed; RCTs comparing different drug regimens have mostly found no significant difference between regimens (moderate-quality evidence).

Note

For HIV-infected women who present late for delivery, post-exposure antiretroviral prophylaxis limited to infants 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 31 .

Benefits:

We found one systematic review (search date 2006, 18 RCTs, 14,398 people) [26] and three subsequent RCTs (reported in 4 publications). [27] [28] [29] [30] For full details of the RCTs, see table 1, p 22 , which presents a comprehensive overview of the individual RCTs. 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. Ideally, all studies should report standardised outcome measures, the most relevant of which is HIV-free survival rate at 2 years. Unfortunately, this is rarely reported.

Antiretroviral drugs in a breastfeeding population:

Antiretroviral drugs versus placebo (breastfeeding population):

The systematic review identified three RCTs. [31] [32] [33] Two RCTs identified by the review assessed maternal prophylaxis with zidovudine. [31] [32] One RCT found that zidovudine given to mothers from 36 weeks' gestation and in labour significantly reduced HIV infection in infants at 4 to 8 weeks and at 3 to 4 months compared with placebo. [31] The RCT also found that zidovudine significantly decreased infant mortality at 1 week and at 3 to 4 months compared with placebo, but found no significant difference in stillbirth between groups. The second RCT assessing maternal prophylaxis found that zidovudine given to mothers from 36 to 38 weeks' gestation, in labour, and for 7 days after delivery significantly reduced HIV infection in infants at up to 18 months. [32] However, the RCT found no significant difference in infant mortality at up to 18 months, or in stillbirth.

The third RCT was a 4-arm RCT that compared three different treatments versus placebo. [33] The three treatment groups were: zidovudine plus lamivudine for the mother from 36 weeks' gestation and during labour, followed by zidovudine plus lamivudine for 1 week after birth for both mother and infant; zidovudine plus lamivudine for the mother at labour onset and for mother and infant until 1 week after birth; and zidovudine plus lamivudine given to only mothers at onset of labour

until delivery. [33] 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 to 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 to 8 weeks, or in stillbirth. The RCT also found no significant difference between zidovudine plus lamivudine given to only the mother at onset of labour until delivery and placebo in HIV infection, infant mortality, or stillbirth.

Different durations of regimens using the same antiretroviral drugs versus each other (breastfeeding population):
The systematic review found one RCT. [34] The RCT found no significant difference between zidovudine given to only the mother 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 to 8 weeks, 6 months, or 18 months.

Different antiretroviral regimens versus each other (breastfeeding population):
The systematic review identified one RCT published in two papers, [35] [36] and we found three subsequent RCTs (reported in 4 publications). [27] [28] [29] [30] The RCT identified by the review, published in two papers, found that HIV infection was significantly less at 3 to 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 first subsequent RCT compared single-dose nevirapine versus placebo in women who received zidovudine from 34 weeks' gestation. [27] All infants received single-dose nevirapine at birth and zidovudine from birth for 1 month. The RCT 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 2 x 2 factorial design also comparing formula feeding versus breastfeeding plus antiretrovirals; see option on different methods of infant feeding, p 11 ; results published in a separate paper. [37]

The second subsequent RCT compared zidovudine given during labour versus placebo in mothers and infants who received single-dose nevirapine. [28] The RCT found no significant difference between groups in the combined outcome of HIV infection or death at 6 weeks. The RCT was terminated at the first interim analysis, as it was unable to recruit sufficient numbers of participants to detect the prespecified difference of 5% in the primary outcome.

The third subsequent RCT (reported in 2 publications) assessed the effects of adding a single dose of tenofovir and emtricitabine (TDF/FTC) to short-course zidovudine (from 32 weeks' gestation) and intrapartum nevirapine. [29] [30] The RCT found no significant difference between addition of TDF/FTC and no TDF/FTC in HIV transmission rate at 6 weeks' postpartum. However, mother-to-child transmission (MTCT) of HIV infection was not the primary outcome of the RCT: the RCT was designed to assess the effects of adding TDF/FTC on viral resistance to non-nucleoside reverse transcriptase inhibitors in women given intrapartum nevirapine.

Antiretroviral drugs in a non-breastfeeding population:
Antiretroviral drugs versus placebo (non-breastfeeding population):
The systematic review identified three RCTs. [38] [39] [40] The first RCT found that zidovudine given to mothers at 14 to 34 weeks' gestation and through labour, and to infants for up to 6 weeks, significantly reduced HIV infection at 18 months compared with placebo. [38] However, it found no significant difference between treatments in infant mortality or stillbirth.

Two later RCTs identified by the review assessed the effects of maternal prophylaxis. [39] [40] One RCT found that zidovudine given to mothers from 36 weeks' gestation and in labour significantly reduced HIV infection at 6 months compared with placebo. [39] It found no significant difference between antiretroviral prophylaxis and placebo in rate of stillbirth or infant mortality. However, the other small RCT found no significant difference between placebo and zidovudine given to mothers alone from 38 weeks' gestation and in labour in HIV infection at 6 months or in rate of stillbirths. [40]

Different durations of regimens using the same antiretroviral drugs versus each other (non-breastfeeding population):
The systematic review identified one RCT reporting on our outcomes of interest. [41] The RCT identified by the review compared 4 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, and for 3 days 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). [41] The short-short group was discontinued at the first interim analysis. The RCT was designed to assess the effects of various treatment regimens on reduction of perinatal MTCT of HIV and so we have reported the RCT here: for extended treatment regimens, data were not reported separately for infants who were HIV-negative at birth. The RCT found no significant difference between long-long and short-long regimens in rate of MTCT of HIV infection at 6 months, but found a significantly lower rate of MTCT of HIV infection with long-short compared with short-long regimens. There was no significant difference in infant mortality between regimens.

Different antiretroviral regimens versus each other (non-breastfeeding population):
The review identified 4 RCTs meeting our reporting criteria, one of which included both non-breastfeeding and breastfeeding women. [42] [43] [44] [45] The first RCT found no significant difference in HIV infection at 4 to 8 weeks between adding nevirapine to standard antiretroviral treatment (at the 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 included both breastfeeding and non-breastfeeding women (majority of women did not breastfeed). [43] The RCT found no significant difference in rate of HIV infection in infants or in rate of infant mortality at 4 to 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). [43]

The third RCT identified by the review found no significant difference in HIV infection at 4 to 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 1 week. [44]

The fourth RCT found no significant difference in rates of infant HIV infection or mortality at 6 months between stavudine and zidovudine, between didanosine and zidovudine, or between stavudine plus didanosine and zidovudine. [45]

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". [26]

We found one systematic review (search date 2005, 21 RCTs and retrospective case series, 4740 pregnant women with HIV) that examined hepatotoxicity associated with nevirapine given for the prevention of MTCT. [46] The review compared short-course (4 days or less) versus long-course (5 days or more) nevirapine-based antiretroviral regimens: the review did not report data separately for breastfeeding and non-breastfeeding populations. The review found that the proportion of women who developed hepatotoxicity was significantly smaller with a short course of nevirapine-based treatment compared with a long-course of treatment (grade 1–2 hepatotoxicity [1119 women in this analysis]: 2/323 [0.6%] with short course *v* 56/796 [7%] with long course: grade 3–4 hepatotoxicity: 7/3031 [0.2%] with short course *v* 75/1709 [4%] with long course; P <0.001 for both comparisons). However, the review found no significant difference between short- and long-course regimens in the rate of hepatotoxicity in neonates born to women treated with nevirapine before delivery (grade 3–4 hepatotoxicity, 3074 neonates in this analysis: 22/2801 [0.8%] with short course *v* 3/273 [1%] with long course; P <0.72).

Antiretrovirals in a breastfeeding population:
Different antiretroviral regimens versus each other (breastfeeding population):
The first subsequent RCT that compared nevirapine versus placebo reported that toxicity rates were low in both mothers and infants. [27] The RCT did not report comparative data for adverse effects. The RCT reported that, between study entry and 3 months after birth, 20 women had a life-threatening event. Of the infants, 12 discontinued treatment with zidovudine before 30 days of age because of adverse effects (most commonly anaemia or neutropenia). Of the infants receiving single-dose nevirapine, 0.7% (5/694) had a serious or life-threatening adverse effect that was determined to be potentially associated with nevirapine.

The second subsequent RCT gave no information on adverse effects. [28]

The third subsequent RCT found no significant difference between addition of TDF/FTC and no TDF/FTC in the proportion of mothers with a serious adverse effect (defined as fatal, life-threatening,

requiring admission to hospital, or resulting in persistent or substantial disability) at 2 weeks after delivery (7/198 [4%] with TDF/FTC *v* 9/199 [5%] with no TDF/FTC; P = 0.800). [29] [30]

A further report of one RCT [41] identified by the review assessed the effects on haematological parameters of longer-term treatment with zidovudine (from 28 weeks' gestation) versus shorter term treatment (from 35 weeks' gestation). [47] The RCT found that a significantly larger proportion of women in the group receiving zidovudine from 28 weeks' gestation had anaemia at 32 and 35 weeks' gestation compared with women in the group not yet exposed to zidovudine (received zidovudine from 35 weeks' gestation) (1436 women; 32 weeks: 63.5% with zidovudine from 28 weeks' gestation *v* 47% with zidovudine from 35 weeks' gestation; P <0.001; 35 weeks: 58.6% with zidovudine from 28 weeks *v* 40.1% with zidovudine from 35 weeks' gestation; P <0.001; absolute numbers not reported). [47] However, there was no significant difference between groups in proportion of women with anaemia at delivery (39.5% with zidovudine from 28 weeks' gestation *v* 35.0% with zidovudine from 35 weeks' gestation; P = 0.10). The RCT found no significant difference between treatment with zidovudine started at 28 weeks' gestation and started at 35 weeks' gestation in rate of leukopenia, or neutropenia at either 35 weeks' gestation (leukopenia: 1.1% with zidovudine from 28 weeks' gestation *v* 0.6% with zidovudine from 35 weeks' gestation; P = 0.40; neutropenia: P = 0.5; absolute numbers not reported for either outcome) or at delivery (leukopenia: 1.4% with zidovudine from 28 weeks' gestation *v* 0.8% with zidovudine from 35 weeks' gestation; P = 0.44; neutropenia: 1.0% with zidovudine from 28 weeks' gestation *v* 0.5% with zidovudine from 35 weeks' gestation; P = 0.35; absolute numbers not reported for either outcome).

Antiretrovirals in a non-breastfeeding population:

Antiretrovirals versus placebo (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. [38] In the RCT using this regimen, the frequency of anaemia (Hb <9.0 g/dL) in the first 6 weeks of life was significantly higher in infants receiving zidovudine compared with placebo (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 an Hb <7.0 g/dL. The anaemia resolved by 12 weeks of age.

Comment:

Resistance mutations:

The emergence of resistance mutations after 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.

One systematic review (search date 2005, 31 studies; the review included RCTs, controlled clinical trials, and observational studies, many of which were reported as conference abstracts) reported that the rate of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in women after a single dose of nevirapine measured at 6 to 8 weeks' post treatment ranged from 8.5% to 69.2% (14 studies). [48] The review also found that resistance prevalence varied with time since treatment, with resistance decreasing over time. Women exposed to single-dose nevirapine were at higher risk of treatment failure if they started antiretroviral therapy within 6 months; the risk diminished after 6 months. [48] For infants born to women who took antiretroviral drugs for MTCT (mostly single-dose nevirapine), the review found rates of resistance to NNRTIs in untreated infants at 6 weeks' postpartum of between 36% and 50% (data from 8 studies).

The use of short-course combination drugs with postpartum tails, the use of highly active antiretroviral treatment (HAART) or the addition of intrapartum tenofovir and emtricitabine (TDF/FTC) may offer improved protection against the emergence of drug resistance. [29] [49] One RCT assessing the effects of adding a single dose of tenofovir and emtricitabine (TDF/FTC) to short-course zidovudine (from 32 weeks' gestation) and intrapartum nevirapine found that maternal resistance to non-nucleoside reverse transcriptase inhibitors at 6 weeks after delivery was significantly lower in the group who had received intrapartum TDF/FTC compared with the group that received zidovudine and single-dose nevirapine alone (20/173 [12%] with TDF/FTC *v* 41/166 [25%] with no TDF/FTC; RR 0.47, 95% CI 0.29 to 0.76; P = 0.002). [29] One RCT that assessed the development of resistance in women who had received a single dose of nevirapine at the onset of labour was initially reported as a summary and has since been published in full; this RCT will be assessed for inclusion at the next update. [50]

Clinical guide:

For HIV-positive pregnant women who are not in need of antiretroviral treatment for their own health, the World Health Organization (WHO) recommends that prophylaxis with antiretroviral drugs be started from as early as 14 weeks' gestation, or as soon as possible if women present late in pregnancy, in labour, or at delivery. [51] WHO recommends two treatment regimens: (1) antiretroviral prophylaxis with daily zidovudine from as early as 14 weeks' gestation, with a single dose of nevirapine at onset of labour, followed by zidovudine and lamivudine given during labour and de-

livery and for 1 week post delivery; for this regimen, WHO recommends that breastfeeding infants receive daily nevirapine until 1 week after the cessation of breastfeeding, and that non-breastfeeding infants be given nevirapine or zidovudine for 6 weeks; (2) maternal prophylaxis with triple antiretroviral therapy from 14 weeks' antepartum to 1 week after cessation of breastfeeding, with breastfeeding infants receiving daily nevirapine for 6 weeks and non-breastfeeding infants receiving nevirapine or zidovudine for 6 weeks.

OPTION ANTIRETROVIRAL DRUGS TO PREVENT POSTPARTUM TRANSMISSION OF HIV

HIV transmission

Different short-term antiretroviral regimens versus each other We don't know how different regimens of short-term antiretroviral prophylaxis (1–6 weeks) compare with each other at reducing infant mortality in children who were HIV negative at birth; we found inconsistent results across RCTs (low-quality evidence).

Short-term antiretroviral regimens versus extended antiretroviral regimens Extended prophylaxis (6–14 weeks; various regimens) for the infant in the postpartum period seems more effective than single-dose regimens or usual care at reducing the rate of HIV transmission at 6 weeks reducing rate of HIV transmission at 6 weeks, but we don't know how they compare in the longer term (6–9 months) (moderate-quality evidence).

Infant mortality

Different short-term antiretroviral regimens versus each other We don't know how different regimens of short-term antiretroviral prophylaxis compare with each other at reducing infant mortality in children who were HIV negative at birth; we found inconsistent results across RCTs (low-quality evidence).

Short-term antiretroviral regimens versus extended antiretroviral regimens We don't know how extended antiretroviral prophylaxis regimens compare with shorter regimens at reducing infant mortality in children who were HIV negative at birth; the RCTs identified had inconclusive results (moderate-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, see table, p 31 .

Benefits:

We found one systematic review (search date 2006, 18 RCTs, 14,398 people), [26] assessing antiretroviral drugs in mother-to-child transmission (MTCT), and two subsequent RCTs. [52] [53] For the purposes of our review, we have reported studies in this option in which infants were found to be HIV negative at birth and the RCTs were designed to assess the effects of antiretroviral treatment on prevention of postpartum (including early postpartum) MTCT of HIV infection. For full details of the RCTs, see table 1, p 22 , which presents a comprehensive overview of the individual RCTs. 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. Ideally, all studies should report standardised outcome measures, the most relevant of which is the 2-year HIV-free survival rate. Unfortunately, this is rarely reported.

Different short-term antiretroviral regimens versus each other:

The review [26] identified three RCTs that reported on the rate of HIV transmission in infants who were HIV negative at birth. [54] [55] [56] The first RCT identified by the review found that rate of HIV infection at 4 to 8 weeks in infants who were breastfed was significantly lower with single-dose nevirapine plus zidovudine (1 week) given to infants postpartum compared with nevirapine alone given to infant postpartum but found no significant difference between groups in infant mortality. [54]

The second RCT identified by the review found no significant difference in HIV infection or infant mortality at 4 to 8 weeks between postpartum nevirapine plus zidovudine (nevirapine given to infant within 72 hours, and zidovudine given to infants for 1 week) compared with nevirapine alone (given to infants within 72 hours) in a subgroup of infants who were HIV negative at birth; infants were breastfed. [55] All mothers received a single dose of nevirapine at onset of labour.

The third RCT identified by the review found no significant difference in HIV infection or infant mortality at 3 to 4 months between nevirapine (to infant postpartum) and zidovudine (for 6 weeks to infant). [56] The RCT was designed to assess the effects of treatments on prevention of postuterine transmission (defined as intrapartum or early postpartum); although the primary outcome of the RCT was HIV infection in infants who were HIV negative at birth, as the RCT was not assessing the effects of postpartum infection we report the RCT here. Women had received no prior antiretroviral treatment. The RCT included breastfeeding women (10% of infants were breastfed).

Short-term antiretroviral regimens versus extended antiretroviral regimens:
The first subsequent RCT pooled data from three sites in Ethiopia, India, and Uganda. [52] The RCT compared intrapartum single-dose nevirapine for mother plus single-dose nevirapine for the infant (usual care) versus usual care plus extended-dose nevirapine for 6 weeks in breastfed infants: infants were HIV-negative at birth. The RCT found that extended-dose nevirapine significantly reduced rate of HIV transmission at 6 weeks' postpartum compared with single-dose nevirapine. However, there was no significant difference between groups in the primary outcome of HIV infection at 6 months, although the rate of infection was lower in the extended-dose nevirapine group (see table 1, p 22). The RCT found a significantly lower rate of infant mortality at 6 months in the extended nevirapine group compared with the single-dose nevirapine group; there was no significant difference between groups in mortality at 6 weeks. The RCT may have been underpowered to detect a clinically significant difference between groups in HIV transmission at 6 months. The RCT reported that the three RCTs were initially designed as independent RCTs, but were later combined. There were differences among the three sites in usual care: in Ethiopia and Uganda, usual care was single-dose nevirapine, while in India, maternal zidovudine or other antiretroviral therapy was optional.

The second subsequent RCT compared three treatments in breastfeeding infants who were HIV negative at birth (tested negative within first 48 hours): single-dose nevirapine plus 1 week of zidovudine (control regimen) versus control regimen plus nevirapine for 14 weeks (extended nevirapine) versus control regimen plus nevirapine and zidovudine for 14 weeks (extended dual prophylaxis). [53] The RCT found that both extended prophylaxis regimens significantly reduced MTCT of HIV at 9 months compared with control (see table 1, p 22). The RCT found no significant difference between the extended nevirapine regimen and the extended dual-prophylaxis regimen in proportion of infants with HIV infection at 9 months. The RCT found no significant difference in mortality at 9 months between either of the extended prophylaxis regimens and control, or between the extended nevirapine regimen and the extended dual prophylaxis regimen. All women received intrapartum single-dose nevirapine.

Harms:

Different short-term antiretroviral regimens versus each other:
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". [26]

Short-term antiretroviral regimens versus extended antiretroviral regimens:
The first subsequent RCT reported that serious adverse effects were common but found no significant difference between extended-dose nevirapine and single-dose nevirapine in the proportion of infants with a serious adverse effect (proportion of infants with a grade 3 or 4 adverse effect: 393/986 [40%] with extended dose nevirapine *v* 346/901 [38%] with single-dose nevirapine; P = 0.54). [52]

The second subsequent RCT found no significant difference among the groups in the proportion of infants experiencing a serious adverse effect that was designated as probably related to a study drug (5/997 [0.5%] with extended dual prophylaxis *v* 6/1016 [0.6%] with extended nevirapine *v* 2/1003 [0.2%] with control; P = 0.42). [53] However, there was a significant difference among groups in the rate of adverse effects designated as possibly related to a study drug (62/997 [6.2%] with extended dual prophylaxis *v* 44/1016 [4.3%] with extended nevirapine *v* 37/1003 [3.6%] with control; P = 0.02 for among group difference). The most common serious adverse effect in the extended-dual prophylaxis group was neutropenia.

Also, see harms on antiretroviral treatments to prevent intrauterine or intrapartum HIV MTCT, p 4 .

Comment:

Two large RCTs assessing the effects of various regimens of antiretroviral treatments (for mother and infant) on the prevention of MTCT postpartum were published subsequent to our search date. [57] [58] At this time, we report the key findings of the RCTs: at the next update, the RCTs will be assessed in the context of the other evidence presented.

One RCT (2369 HIV-positive breastfeeding women with CD4 >250 cells/mm^3; Malawi) evaluated extended antiretroviral drug treatment for both mother and infant versus no extended postnatal antiretroviral regimen. [57] All mothers in labour and their newborn infants received a single dose of nevirapine. All mothers and infants were also given 1 week of zidovudine plus lamivudine after delivery. Women/infant pairs were then randomised to one of three prophylaxis strategies during breastfeeding: no extended antiretroviral prophylaxis (668 pairs); 6 months of daily infant nevirapine (852 infants); or 6 months of daily maternal antiretroviral treatment with zidovudine, lamivudine and lopinovir/ritonavir (849 women). In infants who were HIV-negative at 2 weeks, the RCT found significantly higher risk of transmission of HIV from mother to child at 28 weeks in the group not

receiving extended prophylaxis as compared with the group in which mothers received extended treatment (5.7% with no extended antiretroviral prophylaxis *v* 4.1% with extended maternal prophylaxis; P = 0.009) and the group in which infants received extended treatment (5.7% with no extended antiretroviral prophylaxis *v* 2.6% with extended infant prophylaxis; P <0.001). The study was not powered to compare MTCT between the two extended prophylaxis arms.

The second RCT (560 HIV-positive women with >200 CD4 cells/mm^3) compared two different extended prophylaxis regimens given to women during pregnancy and breastfeeding. [58] Women were randomised between 26 and 34 weeks' gestation to receive one of two regimens: zidovudine plus lamivudine plus abacavir (NRTI group) or zidovudine plus lamivudine plus lopinovir/ritonavir (PI group). The women continued the regimen during 6 months of breastfeeding; women were counselled to wean at 6 months. There was an additional observational arm of 170 women eligible for lifetime treatment (CD4 <200 cells/mm^3) who were treated with zidovudine plus lamivudine plus nevirapine. Infants received single-dose nevirapine at birth followed by zidovudine for 4 weeks. The RCT found that 8/709 (1%) infants were infected with HIV, 6 in utero and two postnatally, both in the NRTI arm. The study was not powered to detect significant differences in MTCT between the treatment arms but was powered to detect differences in viral suppression (<400 copies/mm) between the randomised arms. There were no significant differences between the NRTI and PI groups in viral suppression at delivery (96% with NRTI *v* 93% with PI; 95% CI for percentage differences, –2% to +10%), or viral suppression throughout breastfeeding (92% with NRTI *v* 93% with PI; 95% CI for percentage differences, –8% to +6%).

Clinical guide

Evidence from prospective cohort studies indicates that infant prophylaxis for the full duration of breastfeeding reduces MTCT. One prospective cohort study (398 infants born to HIV-positive women in Tanzania) found that treatment of infants with prophylactic antiretroviral drugs (for a maximum of 6 months) during breastfeeding led to a cumulative risk of MTCT of HIV at 6 months of 4.9% (95% CI 2.7% to 7.1%). [59] In infants who were HIV negative at 6 weeks (380 infants), the cumulative risk of MTCT of HIV from 6 weeks to 6 months was 1.2% (95% CI 0% to 2.4%). Infants received zidovudine plus lamivudine from birth to 1 week of age, followed by lamivudine alone during breastfeeding: exclusive breastfeeding and short weaning period were reported by most mothers.

Maternal treatment provided while breastfeeding may also reduce postnatal MTCT, as demonstrated in an observational cohort study carried out in Rwanda. [60] Of 532 first-liveborn infants, only one infant in the breastfeeding group became infected between 3 and 7 months' follow-up: 6 other infants in the study were infected in utero. This infection rate corresponds to a 9-month cumulative risk of postnatal infection with breastfeeding of 0.5% (95% CI 0.1% to 2.4%; P = 0.24). All women received a highly active antiretroviral treatment (HAART) regimen of stavudine, lamivudine, and nevirapine from 28 weeks' gestation after which they then chose one of two feeding options: breastfeeding with continued HAART either for life (in eligible women, CD4+ <350 cells/mm^3) or through weaning at 6 months for those not eligible for lifetime treatment; or feeding with formula with continued HAART only for those eligible for lifetime treatment. Of the 532 infants, 227 (43%) were breastfed and 305 (57%) were formula fed.

Another cohort study (501 HIV-infected pregnant women in Tanzania) found that the cumulative incidence of HIV infection at 18 months in infants whose mothers who received HAART throughout breastfeeding was 6.0% (95% CI 3.7% to 8.3%); the cumulative incidence of death or HIV infection was 13.6% (95% CI 10.3% to 16.9%) at 18 months. [61] Women received an ART regimen of zidovudine plus lamivudine plus nevirapine, starting at 34 weeks' gestation (nevirapine replaced with nelfinavir for women with adverse reactions to nevirapine and in 2005 for all women with CD4+ >200 cells/mm^3). All women continued ART through 6 months of breastfeeding and continued beyond that if they were eligible for lifetime treatment (CD4+ <200 cells/mm^3 at initiation). Women were counselled to exclusively breastfeed and to wean abruptly between 5 and 6 months. The authors of the RCT noted that the transmission they observed was about half that of the breastfeeding arm of the Petra trial.

OPTION DIFFERENT METHODS OF INFANT FEEDING

HIV transmission

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

Formula feeding plus antiretrovirals compared with breastfeeding plus antiretrovirals for infants Formula feeding plus zidovudine (for 1 month) for infants seems more effective than breastfeeding plus zidovudine (for 6 months) for infants at reducing rate of transmission of HIV infection at 7 months (moderate-quality evidence).

Early cessation of breastfeeding compared with prolonged breastfeeding Early cessation of breastfeeding seems no more effective than prolonged breastfeeding at reducing the rate of transmission of HIV infection (moderate-quality evidence).

HIV-free survival

Formula feeding compared with breastfeeding alone Where formula feeding is safe and feasible, formula feeding seems more effective at improving HIV-1-free survival (moderate-quality evidence).

Early cessation of breastfeeding compared with prolonged breastfeeding Early cessation of breastfeeding seems no more effective than prolonged breastfeeding at improving the rate of HIV-free survival at 2 years (moderate-quality evidence).

Infant mortality

Formula feeding compared with breastfeeding alone Formula feeding and breastfeeding alone seem to be equally effective at reducing infant mortality at 24 months (high-quality evidence).

Formula feeding plus antiretrovirals compared with breastfeeding plus antiretroviral drugs for infants Formula feeding plus zidovudine (for 1 month) for infants seems less effective than breastfeeding plus zidovudine (for 6 months) for infants at reducing cumulative infant mortality at 7 months; however, the two feeding methods seem equally effective at reducing cumulative infant mortality at 18 months (moderate-quality evidence).

Early cessation of breastfeeding compared with prolonged breastfeeding Early and rapid cessation of breastfeeding may be less effective than prolonged breastfeeding at reducing infant mortality at 24 months in children in HIV-endemic areas and who are diagnosed as HIV positive before 4 months of age (low-quality evidence).

Note

We found no direct information from RCTs 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 31 .**

Benefits:

Formula feeding versus breastfeeding alone:

We found no systematic review but found one RCT (425 HIV-1 seropositive women with access to clean water and health education in Kenya) reported in two publications. [5] [62] The RCT compared the effects of formula feeding versus breastfeeding on HIV infection rates in babies. [5] It found that formula feeding significantly reduced the proportion of infants with HIV at 24 months compared with breastfeeding (31/205 [15%] with formula feeding *v* 61/197 [31%] with breastfeeding; RR 0.49, 95% CI 0.33 to 0.72; NNT 7, 95% CI 5 to 13). The RCT found that most mother-to-child transmission (MTCT) through breastfeeding occurred in the early stages of breastfeeding, with 63% of overall risk difference having occurred by 6 weeks of age, and 75% by 6 months. The RCT found no significant difference between the two groups in mortality at 24 months (39/204 [19%] with formula feeding *v* 45/197 [23%] with breastfeeding; RR 0.84, 95% CI 0.57 to 1.23). [5] However, the RCT found that HIV-1-free survival at 2 years was significantly higher with formula compared with breastfeeding (58% with breastfeeding *v* 70% with formula feeding; P = 0.02; absolute numbers not reported).

Formula feeding plus antiretroviral drugs versus breastfeeding plus antiretroviral drugs for infants:

We found one open-label RCT (1200 women from 4 district hospitals in Botswana) comparing formula feeding versus breastfeeding plus antiretroviral drugs. [37] The RCT had a 2 x 2 factorial design, and also compared single-dose nevirapine versus placebo given to women during labour (see option on antiretroviral drugs, p 4 ; results published in a separate paper [27]). In the comparison reported here, infants were randomised to either formula feeding from birth plus zidovudine for 1 month or breastfeeding plus zidovudine for 6 months. At 7 months, the RCT found that HIV infection rates were significantly lower in formula-fed infants than in breastfed infants (cumulative HIV infection rate: 5.6% with formula feeding plus zidovudine *v* 9% with breastfeeding plus zidovudine; rate difference −3.4%, 95% CI −6.4% to −0.4%; P = 0.04; absolute numbers not reported). Although the RCT found that cumulative infant mortality at 7 months was significantly higher with formula feeding compared with breastfeeding (9.3% with formula feeding plus zidovudine *v* 4.9% with breastfeeding plus zidovudine; rate difference 4.4%, 95% CI 1.5% to 7.4%; P = 0.003; absolute numbers not reported), there was no significant difference between groups in this outcome at 18 months (10.7% with formula feeding plus zidovudine *v* 8.6% with breastfeeding plus zidovudine; rate difference +2.2%, 95% CI −1.2% to +5.6%; P = 0.21; absolute numbers not reported). [37]

Exclusive breastfeeding versus mixed feeding:

We found no systematic review or RCTs.

Early cessation of breastfeeding versus prolonged breastfeeding:
We found one RCT (958 HIV-positive pregnant women in Zambia; the RCT enrolled 1435 women and randomised women who were breastfeeding their infants at 1 month postpartum) that compared early, abrupt cessation of breastfeeding (at 4 months) versus prolonged breastfeeding (standard practice). [63] Because of ethical considerations of randomising children to replacement feeding (increased risk of infection in non-breastfed infants in Zambia) or non-exclusive breastfeeding (increased risk of HIV infection) from birth, the RCT randomised women to behavioural programmes that encouraged either exclusive breastfeeding to 4 months followed by abrupt weaning of infants (intervention group) or continued breastfeeding until the mother chose to wean (control group). The RCT found no significant difference between early, abrupt weaning and continued breastfeeding in rate of HIV transmission from mother to child at 24 months (21% with abrupt weaning *v* 26% with continued breastfeeding; P = 0.11; absolute numbers not reported), or in HIV-free survival at 24 months (primary outcome: 68% with abrupt weaning *v* 64% with continued breastfeeding; P = 0.13; absolute numbers not reported). In a subgroup analysis of children who were diagnosed as HIV-positive before 4 months of age and who were alive at 4 months (152 children), the RCT found a significantly higher rate of mortality at 24 months in the early weaning group compared with the continued breastfeeding group (74% with abrupt weaning *v* 55% with continued breastfeeding; P = 0.007; absolute numbers not reported). The RCT highlighted that compliance with early weaning was low, reporting that only 69% of women in the early weaning group had stopped breastfeeding at 5 months. Another issue highlighted by the RCT that could complicate interpretation of results was sooner than expected termination of breastfeeding in the control group; 7.4% of women in the control group had stopped breastfeeding by 5 months, and 34% by 12 months. The median duration of breastfeeding was 4 months in the early cessation group and 16 months in the control group. Women in the intervention group were supplied with a 3-month supply of infant formula and fortified weaning cereal.

Heat or microbicidal treatment of expressed breast milk:
We found no systematic reviews or RCTs.

Harms:

Formula feeding versus breastfeeding alone:
In the Kenyan RCT, [5] a follow-up report examined the impact of breastfeeding on postpartum maternal mortality. [64] Mortality in the first 2 years postpartum was significantly higher in the breastfeeding compared with the formula group (cumulative probability of death: 11% with breastfeeding *v* 4% with formula feeding; P = 0.02; absolute numbers not reported).

One individual patient-data meta-analysis evaluated results from 4237 women with HIV and who had given birth; 162 (4%) died within 18 months after delivery. [65] The study found no significant difference in risk of death during the 18-month period after delivery between "never" breastfeeding and having "ever" breastfed (4237 women in analysis: HR 0.49, 05% CI 0.23 to 1.06).

Formula feeding plus antiretroviral drugs versus breastfeeding plus antiretroviral drugs for infants:
The RCT found a significant increase in grade 3 or higher laboratory abnormalities associated with zidovudine toxicity when comparing breastfeeding plus zidovudine versus formula feeding (25% with breastfeeding plus zidovudine *v* 15% with formula; P <0.001). [37]

Exclusive breastfeeding versus mixed feeding:
We found no RCTs.

Early cessation of breastfeeding versus prolonged breastfeeding:
The RCT gave no information on adverse effects. [63]

Heat or microbicidal treatment of expressed breast milk:
We found no RCTs.

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 breastfeeding has on nutrition, immunity, maternal fertility, and birth spacing are well recognised. An analysis of data from two RCTs of short-course ART in Malawi (total of 2000 women) found that the risk of death at 2 years of age was significantly lower in breastfed compared with non-breastfed infants in HIV-uninfected children (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). [66] A non-randomised intervention cohort study from South Africa (1372 HIV-infected infants [singleton births or first born twin] born to 1372 HIV-infected women) found that breastfed infants who were also given solids were significantly more likely than exclusively breastfed infants to become infected with HIV (HR 10.87, 95% CI 1.51

to 78.00; P = 0.018). The cumulative 3-month mortality was higher in the infants given breast milk and solids compared with exclusively breastfed infants, although the result was of borderline significance (HR 2.06, 95% CI 1.00 to 4.27; P = 0.051). [67]

The World Health Organization recommends that HIV-positive mothers who choose to breastfeed, and if their infants are HIV negative or of unknown HIV status, should exclusively breastfeed for the first 6 months, after which time appropriate complementary foods can be introduced. [68] It also recommends that breastfeeding is continued for the first 12 months of the infant's life, and that breastfeeding is stopped only when an adequate diet without breast milk can be provided. WHO also recommends antiretroviral interventions for mothers and infants throughout breastfeeding to prevent HIV transmission.

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. One non-systematic review summarised evidence that various pasteurisation methods and microbicidal treatment effectively kill HIV in expressed breast milk. [69] Concern that heat treatment of expressed breast milk may have potentially negative effects on the nutritional value, immunologically active components of breast milk, or both seems unsubstantiated when using standardised rapid heating methods.

OPTION ELECTIVE CAESAREAN SECTION

HIV transmission
Compared with vaginal delivery Elective caesarean section seems more effective 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 31 .**

Benefits: We found one systematic review (search date 2004 [70]), which identified one RCT (436 HIV-seropositive women) comparing elective caesarean section at 38 weeks versus vaginal delivery. The RCT included women who received zidovudine during pregnancy and women who did not receive any antiretroviral drugs. The RCT found that caesarean section significantly reduced HIV transmission to infants at 18 months compared with vaginal delivery (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: The review reported no serious adverse effects associated with either caesarean or vaginal delivery. [70] Postpartum fever was significantly more common in women having caesarean section than in those having 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 towards 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. [70]

Comment: About 15% of women withdrew from the RCT or were lost to follow-up. [70] None of the women breastfed, 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 caused by the different delivery methods. [70]

Clinical guide:
Elective caesarean section may reduce the risk of mother-to-child transmission 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, the availability of adequate aseptic conditions, or both.

OPTION IMMUNOTHERAPY

HIV transmission
HIV hyperimmune globulin compared with immunoglobulin without HIV antibody HIV hyperimmune globulin seems no more effective than immunoglobulin without HIV antibody at reducing the risk of transmission of HIV to infants up to 6 months of age from mothers who are also taking zidovudine (moderate-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, **see table, p 31 .**

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. [71] 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: 9/230 [4%] with HIV hyperimmune globulin *v* 13/224 [6%] with immunoglobulin without HIV antibody; RR 0.67, 95% CI 0.29 to 1.55). [71] The low overall transmission rate (5%) in this RCT was much lower than the anticipated rate of >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. [71] It should be noted that the review has been listed online as "obsolete and outdated". [71]

Harms: The RCT found no significant difference between the comparison groups in neonatal haematological toxicity (1 RCT, 506 infants; RR 1.15, 95% CI 0.65 to 2.07). [71]

Comment: **Clinical guide:**
There is no clinical indication for the use of immunoglobulin to reduce the risk of mother-to-child transmission of HIV.

OPTION VAGINAL MICROBICIDES

HIV transmission
Compared with no vaginal microbicides We don't know whether vaginal cleansing with microbicides is more effective than no vaginal microbicides at reducing the risk of HIV transmission to infants (moderate-quality evidence).

Infant mortality
Compared with no vaginal microbicides We don't know whether vaginal cleansing with microbicides is more effective than no vaginal microbicides at reducing infant mortality in either the neonatal or post-neonatal period (moderate-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, **see table, p 31 .**

Benefits: We found one systematic review (search date 2006), which identified two RCTs (708 pregnant women with HIV) comparing vaginal cleansing with microbicides versus no vaginal microbicides. [72] The first RCT compared vaginal cleansing with chlorhexidine (0.2%) versus no cleansing: the RCT was quasi-randomised as participating women were allocated to vaginal cleansing with chlorhexidine or no vaginal cleansing in alternate weeks. The second RCT compared daily vaginal cleansing with benzalkonium chloride capsules versus placebo capsules from week 36 of pregnancy until labour: the RCT was designed and powered to assess the effect on genital ulcers of vaginal cleansing with benzalkonium chloride capsules and was underpowered to detect a clinically significant difference in mother-to-child transmission (MTCT) rate.

The review found no significant difference in the risk of HIV transmission between vaginal cleansing with microbicides and no vaginal microbicides (2 RCTs, 708 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). [72]

The review also found no significant difference between vaginal microbicides and no microbicides in neonatal mortality (1 RCT, 111 infants; 4/55 [7%] with vaginal microbicides *v* 3/56 [5%] with no vaginal microbicides; RR 1.36, 95% CI 0.32 to 5.79), or in infant mortality after the neonatal period (1 RCT, 104 infants; 8/51 [16%] with vaginal microbicides *v* 6/53 [11%] with no vaginal microbicides; RR 1.39, 95% CI 0.52 to 3.71). [72]

Harms: The review found no significant difference between vaginal cleansing with microbicides and no vaginal microbicides in the risk of maternal adverse effects, 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). [72] The review found that vaginal microbicides significantly reduced adverse effects in neonates compared with no microbicides (1 RCT, 108 infants; 21/55 [38%] with vaginal microbicides *v* 45/53 [85%] with no vaginal microbicides; RR 0.45, 95% CI 0.32 to 0.64). [72]

Comment: **Clinical guide:**
The review highlighted that there was insufficient evidence to reach a conclusion on the effectiveness of vaginal microbicides. [72] 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 transmission

Vitamin A compared with placebo or control Vitamin A supplements taken by women with HIV during the antenatal or intrapartum periods, or a single large dose of vitamin A given postpartum to either mothers with HIV, their infants, or to both, seem no more effective than placebo or control at reducing the risk of mother-to-child transmission (MTCT) of HIV infection (moderate-quality evidence).

Infant mortality

Vitamin A compared with placebo or control A single large dose of vitamin A given postpartum to women with HIV may be less effective than no vitamin A supplementation at reducing the composite outcome of HIV infection or mortality at 24 months, and may be no more effective than no vitamin A supplementation when given postpartum to either mothers with HIV plus their infant or to the neonate alone. In breastfed children who are PCR negative for HIV at 6 weeks, maternal plus neonatal postpartum vitamin A supplementation and vitamin A supplementation for the neonate alone may be less effective at reducing the risk of mortality at 24 months (low-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, see table, p 31 .

Benefits:

Vitamin A versus placebo:

We found one systematic review (search date 2008; 4 RCTs, 3033 pregnant women with HIV), which compared vitamin A supplements (with or without multivitamins) versus placebo or no vitamin A supplements (control) during the antenatal and intrapartum periods in HIV-infected women. [74] 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; 292/1014 [29%] with vitamin A *v* 265/1008 [26%] with control; RR 1.05, 95% CI 0.78 to 1.41; see comment below). However, there was significant statistical heterogeneity among the RCTs included in the meta-analysis (P = 0.02); the review did not discuss possible sources of heterogeneity. Of the three RCTs included in the meta-analysis, two RCTs (1124 women) found no significant difference at follow-up in the risk of HIV transmission between vitamin A supplementation and no supplementation, whereas one RCT (898 women) found that vitamin A supplementation was associated with a significant increase in the risk of transmission of HIV infection from mother to child.

The review found no significant difference between supplementation with vitamin A and placebo in infant mortality before 24 months (2 RCTs, 1635 infants; 232/812 [29%] with vitamin A *v* 227/823 [28%] with no vitamin A; RR 1.03, 95% CI 0.88 to 1.20).

We found one RCT (2 x 2 factorial design) assessing the effect of a single large dose of vitamin A given during the postpartum period on child HIV infection and mortality. [75] Vitamin A was given to HIV-positive women alone (400,000 IU), their infants alone (50,000 IU), both mother and infant, or neither mother nor infant: the RCT was excluded by the review as the RCT assessed the effects of postpartum supplementation with vitamin A. [74]

The RCT enrolled 14,110 mother–infant pairs up to 96 hours after delivery: of these pairs, 4495 infants were born to HIV-positive mothers and were included in the analysis. [75] The RCT found no significant difference in rate of mother-to-child transmission (MTCT) of HIV at 24 months in infants who were PCR negative for HIV at baseline (4064 infants) between no vitamin A supplementation (1020 infants) and all three vitamin A supplementation regimens (vitamin A for the mother alone, 1006 infants: difference between groups [in probability of infection] +5.4, 95% CI −0.9 to +13.3; vitamin A for the neonate alone, 1026 infants: difference between groups [in probability of infection] +4.3, 95% CI −1.5 to +10.7; vitamin A for both mother and infant, 1012 infants: difference between groups [in probability of infection] +0.4, 95% CI −5.0 to +6.3; absolute numbers not reported for any group). The RCT found no significant difference in the composite outcome of HIV infection or mortality at 24 months in infants who were PCR negative for HIV at baseline (3708 infants in this analysis) between no vitamin A supplementation and vitamin A supplementation for both mother and infant (HR 1.03, 95% CI 0.87 to 1.22; P = 0.71; absolute numbers not reported) or between no vitamin A supplementation and neonatal vitamin A supplementation (HR 1.17, 95% CI 1.00 to 1.38; P = 0.06; absolute numbers not reported). However, the RCT found that vitamin A supplementation for the mother alone was associated with a significant increase in risk of the composite outcome of HIV infection or mortality at 24 months in infants who were PCR negative for HIV at baseline compared with no vitamin A supplementation (HR 1.19, 95% CI 1.01 to 1.40; P = 0.04; absolute numbers not reported). The RCT found that the timing of infant HIV infection influenced the effect of vitamin A supplementation on mortality. In breastfed children who were PCR negative for HIV at 6 weeks (2876 infants), all three vitamin A regimens approximately doubled the risk of mortality by 24 months, with the difference between no vitamin A supplementation and maternal

plus neonatal vitamin A supplementation (HR 2.05, 95% CI 1.14 to 3.67; P = 0.02; absolute numbers not reported) and between no vitamin A supplementation and vitamin A supplementation for the neonate alone reaching significance (HR 1.89, 95% CI 1.05 to 3.40; P = 0.03; absolute numbers not reported). The difference between maternal vitamin A supplementation and no vitamin A supplementation was of borderline significance (HR 1.82, 95% CI 0.99 to 3.31; P = 0.05; absolute numbers not reported).

Harms:

Vitamin A versus placebo:
The review found no significant difference between supplementation with vitamin A and placebo in maternal mortality (1 RCT, 728 women; 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). [74] The review found no significant difference between vitamin A supplements and no vitamin A in the risk of stillbirth (4 RCTs, 2855 infants; 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), low birth weight (less than 2500 g) (4 RCTs, 2606 infants; 157/1309 [12%] with vitamin A *v* 189/1297 [15%] with no vitamin A; RR 0.83, 95% CI 0.68 to 1.01), or preterm birth before 34 or 37 weeks (preterm birth before 34 weeks: 2 RCTs, 1578 women; 44/793 [5.5%] with vitamin A *v* 50/785 [6.4%] with no vitamin A; RR 0.69, 95% CI 0.24 to 2.00; preterm birth before 37 weeks: 3 RCTs, 2110 women; 182/1071 [17%] with vitamin A *v* 195/1039 [19%] with no vitamin A; RR 0.88, 95% CI 0.65 to 1.19). [74]

The RCT assessing the effects of postpartum vitamin A gave no information on adverse effects of vitamin A supplementation. [75]

Comment:

The RCTs identified by the review [74] were performed because observational studies have found an association in pregnant women between transmission of HIV and low serum levels of vitamin A. [76]

One 4-arm RCT identified by the review [74] enrolled 1078 HIV-infected pregnant women in a double-blind placebo controlled trial in Dar es Salaam, Tanzania, and assessed the effect of multivitamins with or without vitamin A given to mothers with HIV during pregnancy and lactation. [77] The 4 arms in the RCT were: supplementation with vitamin A alone; supplementation with multivitamins excluding vitamin A; supplementation with multivitamins including vitamin A; and placebo. The RCT was of a 2 x 2 factorial design and reported results for multivitamins versus no multivitamin and for vitamin A versus no vitamin A. Samples for testing of HIV status were taken from 453 infants at 6 weeks, out of a possible 962 live births. It found no significant difference between multivitamins (268 women) and no multivitamin (267 women) in HIV transmission to infants at 6 weeks (16% with multivitamins *v* 16% with placebo; RR 1.04, 95% CI 0.65 to 1.66). Long-term follow-up [78] of the RCT [77] found no significant difference between multivitamins and no multivitamin in infant death at 24 months (24% with multivitamins *v* 26% with placebo; RR 0.91, 95% CI 0.71 to 1.17). A separate report of the RCT focused on the effects of multivitamin supplementation on maternal health and HIV disease progression. [79] The RCT found that significantly fewer women taking multivitamins progressed to WHO stage 4 disease compared with those taking placebo (67/271 [25%] with multivitamins *v* 82/267 [31%] with placebo; RR 0.7, 95% CI 0.51 to 0.98).

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.

OPTION MICRONUTRIENT SUPPLEMENTS New

Infant mortality
Compared with placebo Selenium supplements given to pregnant women with HIV during their pregnancy and in the postnatal period may be more effective at reducing infant mortality between 6 weeks and 6 months of age, but they may be no more effective at reducing earlier infant mortality (at up to 6 weeks) (low-quality evidence).

For GRADE evaluation of interventions for HIV: mother-to-child transmission, see table, p 31 .

Benefits:

We found no systematic review or RCT meeting our reporting criteria that assessed the effects of micronutrient supplementation on rate of mother-to-child transmission (MTCT) of HIV.

We found one RCT (915 pregnant women with HIV) comparing maternal selenium supplements given during pregnancy and until 6 months' postpartum versus placebo that reported on infant mortality. [80] The RCT did not report data on MTCT. The RCT found no significant difference between selenium and placebo in infant mortality at 6 weeks (815 infants from single births included in analysis: 2.7% with selenium *v* 2.9% with placebo; RR 0.96, 95% CI 0.42 to 2.17; P = 0.91; absolute numbers not reported). However, the RCT found that selenium supplementation significantly reduced infant mortality between 6 weeks and 6 months compared with placebo (2% with selenium

v 5% with placebo; RR 0.43, 95% CI 0.19 to 0.99; P = 0.048; absolute numbers not reported). It should be noted that the reported confidence interval for the protective effect of selenium on infant mortality comes close to crossing 1 (which would indicate a non-significant finding) and the authors only report infant mortality outcomes at up to 6 months but not at later time periods. Women also received prenatal multivitamins from the time of enrolment until delivery, and a single dose of nevirapine during labour. Infants were given a single dose of nevirapine within 72 hours of birth.

Harms: The RCT gave no information on the adverse effects of selenium supplements. [80]

Comment: We found one RCT (400 women) assessing the effects of zinc supplementation given to mothers with HIV during pregnancy that did not meet our reporting criteria (less than 80% of infants born included in analysis). [81] However, due to a paucity of data, we have decided to report this RCT here. The RCT found no significant difference between zinc supplementation and placebo in the proportion of infants who were HIV positive at birth (0–21days) (286 infants for whom HIV status was known at birth: 6% with zinc *v* 4% with placebo; RR 1.37, 95% CI 0.49 to 3.85; P = 0.26) or in rate of HIV transmission at 6 weeks in infants who were HIV-negative at birth (183 infants followed-up: 8% with zinc *v* 5% with placebo; RR 1.51, 95% CI 0.50 to 4.59; P = 0.46; absolute numbers not reported for either outcome).

Clinical guide:
The evidence from the one RCT found on selenium did not indicate a benefit from maternal selenium supplementation on infant survival, nor did it report data for MTCT of HIV. Based on this evidence and the lack of high-quality studies on the topic in general, micronutrient supplementation is not indicated for preventing MTCT or improving infant survival.

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.

SUBSTANTIVE CHANGES

Micronutrient supplements New option added for which we found one RCT assessing the effects of selenium supplementation. [80] The RCT did not report on prevention of mother-to-child transmission (MTCT) of HIV, but reported on infant mortality. The RCT found that selenium reduced infant mortality between 6 weeks and 6 months; however, the result was of borderline significance. The RCT found no significant difference between selenium and placebo in infant mortality at 6 weeks and maternal mortality at 6 months. As the RCT did not report on MTCT, categorised set as Unknown effectiveness.

Antiretroviral drugs (to prevent intrauterine and intrapartum transmission of HIV) Option restructured to report data on the effects of antiretroviral drugs in the prevention of intrauterine and intrapartum HIV transmission separately from data on antiretroviral drugs for the prevention of postpartum transmission. One RCT (reported in 2 publications) added at update found no significant difference in the rate of HIV transmission from mother to child at 6 weeks' postpartum between adding a single dose of tenofovir and emtricitabine to short-course zidovudine (from 32 weeks' gestation) plus intrapartum nevirapine and zidovudine plus nevirapine alone. [29] [30]

Antiretroviral drugs to prevent postpartum transmission of HIV Option restructured: data on prevention of postpartum transmission reported separately at this update. Three RCTs [54] [55] [56] identified by a systematic review, [26] and two subsequent RCTs added at update found different results on the effectiveness of different antiretroviral treatments for infants postpartum in preventing transmission of HIV infection. [52] [53] Antiretroviral drugs are effective in reducing rate of MTCT of HIV infection, but it is unclear which regimen is the most effective. Categorisation set as Beneficial.

Vaginal microbicides One systematic review added, [72] which supersedes a previously reported review. [73] The added review identified no new evidence on the effects of vaginal microbicides and reached similar conclusions to the previously reported review. [73] The review found no significant difference between vaginal cleansing and no vaginal cleansing in HIV transmission rate, or in infant mortality. [72] The review highlighted that there was insufficient evidence to reach a conclusion on the effectiveness of vaginal microbicides. Categorisation unchanged (Unknown effectiveness).

Vitamin supplements One updated systematic review found no new evidence on the effects of supplementation with vitamin A on preventing mother-to-child transmission. [74] Categorisation unchanged (Likely to be ineffective or harmful).

Different methods of infant feeding One RCT added comparing early, abrupt cessation of breastfeeding (at 4 months) versus prolonged breastfeeding (standard practice). [63] The RCT found no significant difference between early, abrupt weaning and continued breastfeeding in rate of HIV transmission from mother to child at 24 months, or in HIV-free survival at 24 months. In a subgroup analysis of children who were diagnosed as HIV positive before 4 months of age and who were alive at 4 months, the RCT found a significantly higher rate of mortality at 24 months in the early weaning group compared with the continued breastfeeding group. Evidence reassessed at update. The risk of breastfeeding-related HIV transmission needs to be balanced against the multiple benefits that breastfeeding offers. Categorisation changed (from Likely to be beneficial to Trade-off between benefits and harms).

Immunotherapy Large RCT suggests that immunotherapy with HIV hyperimmune globulin confers no benefit in the prevention of mother-to-child transmission of HIV. Evidence re-evaluated and categorisation changed from Unknown effectiveness to Unlikely to be beneficial.

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Disclaimer

TABLE 1 **Summary of randomised controlled trials 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	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
Prevention of intrauterine or intrapartum MTCT: antiretroviral drugs versus placebo in a breastfeeding population					
RETRO-CI [31]	Ivory Coast 1 clinic 280 women	ZDV *v* placebo in mothers **Treatment regimen** *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 **Control** Placebo	**At 4 weeks** 15/122 (12%) with ZDV *v* 26/119 (22%) with placebo RRR 44%, 95% CI 9% to 79% **At 3 months** 19/115 (16%) with ZDV *v* 30/115 (25%) with placebo RRR/efficacy 37%, 95% CI 4% to 70%	**In the first week of life** 1/140 (1%) with ZDV *v* 8/140 (6%) with placebo RR 0.13, 95% CI 0.02 to 0.99 **In the first 3 to 4 months of life** 3/140 (2%) with ZDV *v* 20/140 (14%) with placebo RR 0.15, 95% CI 0.05 to 0.49	7/140 (5%) with ZDV *v* 2/140 (1%) with placebo RR 3.50 95% CI 0.74 to 16.55
DITRAME; Lancet 1999 [32]	Ivory Coast, Burkina Faso Multiple clinics 421 women	ZDV *v* placebo in mothers **Treatment regimen** *Mother* ZDV antepartum orally 300 mg twice daily from 36 to 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 **Control** Placebo	**At 3 to 4 months** RRR 34.00%, 95% CI 6.56% to 61.44% **At 6 months** RRR 35%, 95% CI 10% to 60% **At 12 months** RRR/efficacy 34%, 95% CI 9% to 60% **At 18 months** RRR 30%, 95% CI 3% to 57% Absolute numbers not reported for any timeframe	**In the first week of life** 6/214 (3%) with ZDV *v* 3/217 (1%) with placebo RR 2.03, 95% CI 0.51 to 8.0 **In the first 4 to 8 weeks** 7/214 (3%) with ZDV *v* 4/217 (2%) with placebo RR 1.77, 95% CI 0.53 to 5.97 **In the first 3 to 4 months** 11/214 (5%) with ZDV *v* 15/217 (7%) with placebo RR 0.74, 95% CI 0.35 to 1.58 **In the first 6 months** 17/214 (8%) with ZDV *v* 28/217 (13%) with placebo RR 0.62, 95% CI 0.35 to 1.09 **In the first 12 months** 28/214 (13%) with ZDV *v* 38/217 (18%) with placebo RR 0.75, 95% CI 0.48 to 1.17 **In the first 18 months** 33/214 (15%) with ZDV *v* 42/217 (19%) with placebo RR 0.80, 95% CI 0.53 to 1.21	1/214 (<1%) with ZDV *v* 7/217 (3%) with placebo RR 0.14, 95% CI 0.02 to 1.17

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative risk reduction (RRR)/efficacy	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
PETRA A, B, and C; Lancet 2002 [33]	South Africa, Uganda, Tanzania 5 sites 1797 women	ZDV + 3TC *v* placebo in mothers and infants Breastfeeding and no breastfeeding (74% of infants were breastfed) 4-arm RCT **Petra A** **ZDV + 3TC regimen** *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** **ZDV + 3TC regimen** *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 postpartum for 1 week *Infant* ZDV 4 mg/kg + 3TC 2 mg/kg orally twice daily for 1 week **Petra C** **ZDV + 3TC regimen** *Mother* ZDV 600 mg orally intrapartum at onset of labour then 300 mg every 3 hours until delivery *Infant* No treatment **Control** Fourth arm was placebo	**At 4 to 8 weeks** 7.0% with Petra A *v* 11.6% with Petra B *v* 17.5% with Petra C *v* 18.1% with placebo **Petra A *v* placebo** RRR 63%, 95% CI 41% to 85% **Petra B *v* placebo** RRR 42%, 95% CI 13% to 71% **Petra C *v* placebo** RRR +7%, 95% CI –32% to +46% **At 18 months** Absolute numbers not reported **Petra A *v* placebo** RRR +33%, 95% CI% –12% to +78% **Petra B *v* placebo** RRR +18%, 95% CI –27% to +63% **Petra C *v* placebo** RRR +10%, 95% CI –41% to +61% With prolonged breastfeeding, transmission rates for all groups combined were 80%	**In the first 4 to 8 weeks** **Petra A *v* placebo** 4/475 (1%) with Petra A *v* 9/377 (2%) with placebo RR 0.35, 95% CI 0.11 to 1.14 **Petra B *v* placebo** 8/474 (1.6%) with Petra B *v* 9/377 (2.3%) with placebo RR 0.71, 95% CI 0.28 to 1.81 **Petra C *v* placebo** 11/471 (2.3%) with Petra C *v* 9/377 (2.3%) with placebo RR 0.98, 95% CI 0.41 to 2.34 **In the first 18 months** **Petra A *v* placebo** 37/366 (10%) with Petra A *v* 47/352 (13%) with placebo RR 0.76, 95% CI 0.50 to 1.14 **Petra B *v* placebo** 52/371 (14%) with Petra B *v* 47/352 (13%) with placebo RR 1.05, 95% CI 0.73 to 1.51 **Petra C *v* placebo** 47/368 (12.7%) with Petra C *v* 47/352 (13.3%) with placebo RR 0.96, 95% CI 0.66 to 1.39	**Petra A *v* placebo** 2/475 (0.4%) with Petra A *v* 4/377 (1%) with placebo RR 0.40, 95% CI 0.07 to 2.15 **Petra B *v* placebo** 6/474 (1.3%) with Petra B *v* 4/377 (1.1%) with placebo RR 1.19, 95% CI 0.34 to 4.20 **Petra C *v* placebo** 4/471 (0.8%) with Petra C *v* 4/377 (1.1%) with placebo RR 0.80, 95% CI 0.20 to 3.18

Prevention of intrauterine or intrapartum MTCT: different durations of the same antiretroviral drugs versus each other in a breastfeeding population

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative risk reduction (RRR)/efficacy	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
Thistle 2004; Centr Afr J Med 2004 [34]	Zimbabwe 1 hospital 222 women	Different regimens of ZDV *v* each other **ZDV for mother alone** *Mother* ZDV antepartum 300 mg twice daily from 36 weeks' gestation ZDV intrapartum 300 mg every 3 hours during labour *Infant* Placebo **ZDV for mother and infant** *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 to 8 weeks** 17/90 (19%) with ZDV given to mother alone *v* 14/89 (16%) with ZDV given to mother and infant RRR +17%, 95% CI –42% to +76% **At 6 months** 21/74 (28%) with ZDV given to mother alone *v* 19/73 (26%) with ZDV given to mother and infant RRR +8%, 95% CI –43% to +59% **At 12 months** 22/53 (42%) with ZDV given to mother alone *v* 22/55 (40%) with ZDV given to mother and infant RRR +9%, 95% CI –34% to +52%	**At 4 to 8 weeks** 3/111 (3%) with ZDV given to mother alone *v* 3/111 (3%) with ZDV given to mother and infant RR 1.00, 95% CI 0.21 to 4.85 **At 3 to 4 months** 7/111 (6%) with ZDV given to mother alone *v* 4/111 (4%) with ZDV given to mother and infant RR 1.75, 95% CI 0.53 to 5.81 **At 6 months** 10/111 (9%) with ZDV given to mother alone *v* 5/111 (5%) with ZDV given to mother and infant RR 2.00, 95% CI 0.71 to 5.66 **At 12 months** 10/111 (9%) with ZDV given to mother alone *v* 5/111 (5%) with ZDV given to mother and infant RR 2.00, 95% CI 0.71 to 5.66	None in either group
Prevention of intrauterine or intrapartum MTCT: different antiretroviral regimens versus each other in a breastfeeding population					
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 **NVP arm** *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 to 8 weeks** Estimated rate of HIV transmission: 21.3% with ZDV *v* 11.9% with NVP RRR 41.0%, 95% CI 11.6% to 70.4% **At 3 to 4 months** Estimated rate of HIV transmission: 25.1% with ZDV *v* 13.1% with NVP RRR/efficacy 39%, 95% CI 12% to 66% **At 18 months** Estimated rate of HIV transmission: 25.8% with ZDV *v* 15.7% with NVP RRR/efficacy 39%, 95% CI 14% to 64%	**In the first week of life** 5/313 (2%) with ZDV *v* 2/313 (1%) with NVP RR 2.50, 95% CI 0.49 to 12.79 **At 4 to 8 weeks** 10/313 (3%) with ZDV *v* 4/313 (1%) with NVP RR 2.50, 95% CI 0.79 to 7.89 **At 18 months** 42/313 (13%) with ZDV *v* 34/313 (11%) with NVP RR 1.24, 95% CI 0.81 to 1.89	2/313 (1%) with ZDV *v* 1/313 (<1%) with NVP RR 2.00, 95% CI 0.18 to 21.94

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative risk reduction (RRR)/efficacy	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
Mashi Report 1; AIDS 2006 [27]	Botswana 4 sites Report 1 709 women	NVP *v* placebo during labour **NVP** *Mother* NVP 300 mg 3-hourly during labour **Control** *Mother* placebo In addition: all mothers were given ZDV 300 mg orally twice daily from 36 weeks' gestation + ZDV 300 mg during labour all infants were given 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%, 95% CI –2.4% to +3.8%	**At 4 weeks** 7/345 (2%) with NVP *v* 13/353 (4%) with PL P = 0.26	NR
Thistle 2007; Pediatrics 2007 [28]	Zimbabwe 1 hospital 1140 women randomised, 609 infants included in analysis	ZDV + NVP *v* NVP alone in mothers and infants **NVP alone** *Mother* Single dose nevirapine 200 mg during labour plus zidovudine placebo *Infants* 2 mg/kg NVP within 72 hours of delivery **ZDV + NVP** *Mother* In addition to single dose NVP: ZDV antepartum 300 mg twice daily from 36 weeks gestation ZDV intrapartum 300 mg every 3 hours *Infant* In addition to NVP: ZDV 2 mg/kg orally every 6 hours for 3 days	**HIV infection or death at 6 weeks** 70/297 (24%) with NVP *v* 68/312 (22%) with ZDV+ NVP ARR +1.8% 95% CI –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
Reported in 2 publications [29] [30]	Zambia 2 public health clinics 397 women	Addition of tenofovir and emtricitabine (TDF/FTC) to ZDV plus NVP *v* ZDV plus NVP for mothers and infants **TDF/FTC added to ZDV plus NVP** *Mother* ZDV antepartum 300 mg twice daily from 32 weeks gestation Single-dose NVP 200 mg at onset of labour or during labour if not taken at onset Single dose of TDF (300 mg)/FTC (200 mg) during labour *Infant* 2 mg/kg NVP before discharge ZDV 4 mg/kg twice daily for 7 days **ZDV plus NVP** *Mother and infants* ZDV and NVP given as above	**At 6 weeks** 10/180 (6%) with TDF/FTC *v* 14/175 (8%) with no TDF/FTC OR 0.7, 95% CI 0.3 to 1.6 P = 0.403 HIV transmission rate was not the primary outcome assessed: primary outcome was effect of TDF/FTC on reducing viral resistance to NNRTIs	NR	NR

Prevention of intrauterine or intrapartum MTCT: antiretroviral drugs versus placebo in a non-breastfeeding population

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative risk reduction (RRR)/efficacy	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
PACTG 076; N Engl J Med 1994 [38]	USA, France 60 centres 409 women	ZDV *v* placebo in mothers and infants **ZDV regimen** *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/hour until delivery *Infant* ZDV orally 2 mg/kg every 6 hours for 6 weeks **Control** Placebo given to mothers and infants	**At 18 months** Estimated rate of HIV transmission: 8.3% with ZDV for mother and infant *v* 25.5% with placebo RRR 66%, 95% CI 35% to 97%	**At 18 months** 4/239 (1.6%) with ZDV for mother and infant *v* 3/238 (1.3%) with placebo RR 1.33, 95% CI 0.30 to 5.87	**At 18 months** 0/239 (0%) with ZDV for mother and infant *v* 1/238 (0.4%) with placebo RR 0.33, 95% CI 0.01 to 8.11
Thai-CDC; Lancet 1999 [39]	Thailand 2 hospitals 393 women	ZDV *v* placebo in mothers **ZDV regimen** *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 **Control** Placebo	**At 6 months** Estimated rate of HIV transmission: 9.4% with ZDV *v* 18.9% with placebo RRR 50%, 95% CI 15% to 70%	**In the first 4 to 8 weeks of life** 1/198 (0.5%) with ZDV for mother *v* 2/199 (1.0%) with placebo RR 0.50, 95% CI 0.05 to 5.50	1/198 (0.5%) with ZDV for mother *v* 0/199 (0%) with placebo RR 3.02, 95% CI 0.12 to 73.57
Limpongsanurak; J Med Assoc Thai 2001 [40]	Thailand 3 hospitals 182 women	ZDV *v* placebo in mothers **ZDV regimen** *Mother* ZDV 250 mg orally twice daily from 38 weeks' antepartum 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** Estimated rate of HIV transmission: 14.9% with ZDV *v* 16.3% with placebo RRR +9%, 95% CI –26% to +44%	NR	1/90 (1%) with ZDV *v* 0/92 (0%) with placebo RR 3.07, 95% CI 0.13 to 74.28
Prevention of intrauterine or intrapartum MTCT: different durations of the same antiretroviral drugs versus each other (includes if given to either mother or infant alone) in a non-breastfeeding population					

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative risk reduction (RRR)/efficacy	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
PHPT-1; N Engl J Med 2000 [41]	Thailand 27 sites 1437 women	Various durations of ZDV *v* each other in mothers and infants 4-arm RCT **ZDV long-long (LL)** *Mother* 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 ZDV intrapartum orally 300 mg every 3 hours until delivery *Infant* ZDV for 3 days **ZDV short-long (SL)** *Mother* ZDV from 36 weeks' antepartum ZDV intrapartum orally 300 mg every 3 hours until delivery *Infant* ZDV for 6 weeks **ZDV short-short (SS)** *Mother* ZDV from 36 weeks' antepartum ZDV intrapartum orally 300 mg every 3 hours until delivery *Infant* ZDV for 3 days	**At 6 months** Estimated rates of HIV transmission: 6.5% with LL *v* 4.7% with LS *v* 8.6% with SL *v* 10.5% with SS LL *v* SL RRR +24%, 95% CI –21% to +69% LS *v* SL RRR 45%, 95% CI 2% to 88% SS discontinued at first interim analysis as it did not seem to reduce transmission of HIV	**At 6 months** LL *v* SL 5/419 (1.2%) with LL *v* 5/345 (1.4%) with SL RR 0.82, 9% CI 0.24 to 2.82 LS *v* SL 7/345 (2%) with LS *v* 5/345 (1%) with SL RR 1.38, 95% CI 0.44 to 4.31	LL *v* SL 8/419 (2%) with LL *v* 12/345 (3%) with SL RR 0.55, 95% CI 0.23 to 1.33 LS *v* SL 4/350 (1%) with LS *v* 12/345 (3%) with SL RR 0.33, 95% CI 0.11 to 1.01
Prevention of intrauterine or intrapartum MTCT: different regimens of antiretroviral drugs versus each other in a non-breastfeeding population					
PACTG 316; JAMA 2002 [42]	US, Europe, Brazil, Bahamas Multiple sites 1270 women	NVP *v* placebo in mother and infant All mothers received standard ART at discretion of treating physician **NVP regimen** *Mother* NVP 200 mg orally intrapartum at onset of labour *Infant* NVP 2 mg/kg orally within 72 hours **Control** Placebo	**At 4 to 8 weeks** 9/631 (1.4%) with ART + NVP *v* 10/617 (1.6%) with standard ART alone RRR +13%, 95% –83% to +109% Study stopped early because overall transmission rates were lower than assumed for the study design	**At 4 to 8 weeks** 3/754 (0.4%) with ART + NVP *v* 5/752 (0.7%) with standard ART alone RR 0.60, 95% CI 0.14 to 2.50	1/754 (0.1%) with ART + NVP *v* 0/752 (0%) with standard ART alone RR 2.99, 95% CI 0.12 to 73.33

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative risk reduction (RRR)/efficacy	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
SAINT; J Infect Dis 2003 [43]	South Africa 11 sites 1317 women	ZDV + 3TC *v* NVP in mothers and infants Breastfeeding and no breastfeeding (approximately 45% breastfed at delivery; 30% at 8 weeks) **ZDV arm** *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 postpartum for 1 week *Infant* ZDV 4 mg/kg + 3TC 2 mg/kg orally twice daily for 1 week **NVP arm** *Mother* NVP 200 mg orally intrapartum at onset of labour *Infant* NVP 6 mg orally within 48 hours	**At 4 to 8 weeks** Estimated rates of HIV transmission: 12.3% with NVP *v* 9.3% with ZDV + 3TC RRR +24%, 95% CI –5% to +53% Increased HIV transmission risk in breast-feeding group OR 7, 95% CI 2 to 25	**At 4 to 8 weeks** 19/657 (2.9%) with NVP *v* 19/662 (2.9%) with ZDV + 3TC RR 1.01, 95% CI 0.54 to 1.89	NR
PHPT-2; N Engl J Med 2004 [44]	Thailand 37 sites 1844 women	NVP *v* placebo to mothers and infants in 2 different regimens In addition to NVP: 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** 12/627 (1.9%) with NVP-NVP *v* 17/611 (2.8%) NVP-PL RRR NVP-NVP *v* NVP-PL +29%, 95% CI –26% to +84% Placebo arm discontinued at first interim analysis (HIV transmission rate of 6.5% at interim analysis)	**At 6 months** NVP-NVP *v* NVP-PL 2/724 (0.3%) with NVP-NVP *v* 10/721 (1.3%) NVP-PL RR 0.20, 95% CI 0.04 to 0.91	NVP-NVP *v* NVP-PL 2/724 (0.3%) with NVP-NVP *v* 8/721 (1%) NVP-PL RR 0.25, 95% CI 0.05 to 1.17 Placebo-placebo arm discontinued at first interim analysis

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative risk reduction (RRR)/efficacy	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
Gray 2006; J Acquir Immune Defic Syndr 2006 [45]	South Africa 1 hospital 373 women	d4T alone *v* ddI alone *v* d4T + ddI *v* ZDV (4 arms) *Mother* **d4T alone** d4T 40 mg orally twice daily ante- and intrapartum (from 34–36 weeks' gestation). An additional dose was administered approximately 1 hour before delivery **ddI alone** ddI 200 mg orally twice daily **d4T plus ddI** As for d4T and ddI dosing schedule **ZDV** ZDV 300 mg twice daily *Infant* In all arms, the infant received the same regimen as the mother continued for 6 weeks' postpartum	**At 6 months** 11/91 (12.1%) with d4T *v* 10/94 (10.6%) with ddI *v* 4/88 (4.6%) with d4T + ddI *v* 5/89 (5.6%) with ZDV **d4T *v* ZDV** RRR –116%, 95% CI –280% to +49% **ddI *v* ZDV** RRR –89%, 95% CI –248% to +70% **d4T plus ddI *v* ZDV** RRR +18%, 95% CI –119% to +155%	**At 6 months** **d4T *v* ZDV** 9/93 (10%) with d4T *v* 3/92 (3%) with ZDV RR 2.97, 95% CI 0.83 to 10.61 **ddI *v* ZDV** 6/95 (6%) with ddI *v* 3/92 (3%) with ZDV RR 1.94, 95% CI 0.50 to 7.52 **d4T plus ddI *v* ZDV** 2/93 (2%) with d4T + ddI *v* 3/92 (3%) with ZDV RR 0.66, 95% CI 0.11 to 3.86	NR
Prevention of postpartum MTCT: different short-term antiretroviral regimens versus each other					
NVAZ; Lancet 2003 [54]	Malawi 6 clinics 1119 infants randomised, 1000 infants tested negative for HIV at birth	NVP *v* NVP + ZDV in infants *Infant* Breastfeeding **NVP alone** NVP 2 mg/kg stat oral dose postpartum **NVP + ZDV** NVP as above + ZDV 4 mg/kg twice daily for 1 week	**At 4 to 8 weeks (subgroup analysis of infants who tested negative for HIV at birth)** 34/444 (8%) with NVP + ZDV *v* 51/421 (12%) with NVP RRR 37%, 95% CI 4% to 70%	**At 4 to 8 weeks (all infants)** 15/557 (3%) with NVP + ZDV *v* 12/562 (2%) with NVP RR 1.26, 95% CI 0.60 to 2.67	NR
Taha 2004; JAMA 2004 [55]	Malawi 6 clinics 894 infants born to HIV-positive mothers were randomised; 719 infants were diagnosed as HIV-negative at birth	ZDV + NVP *v* NVP alone in infants NVP 200 mg given to all mothers at onset of labour Breastfeeding **ZDV + NVP** *Infant* NVP 2 mg/kg within 72 hours of delivery plus ZDV 4 mg/kg orally twice daily for 1 week **NVP alone** *Infant* NVP 2 mg/kg within 72 hours of delivery	**At 6 to 8 weeks** **Subgroup analysis of infants who were HIV negative at birth (719 infants)** 23/353 (6.5%) with NVP *v* 25/363 (6.9%) with NVP + ZDV P = 0.88 Estimated rate of HIV transmission in all infants: 14.1% with NVP *v* 16.3% with NVP + ZDV RRR/efficacy +13%, 95% CI –16% to +42% As data based on estimated values, absolute numbers not reported	**At 6 to 8 weeks (all infants, including those that were HIV positive at birth)** 7/448 (13%) with NVP *v* 4/446 (11%) with NVP + ZDV RR 1.74, 95% CI 0.51 to 5.91	NR
Gray 2005; AIDS 2005 [56]	South Africa 3 hospitals 1051 infants randomised (1530 women enrolled)	NVP *v* ZDV in infants (10% of infants were breastfed) *Infant* **NVP** 2 mg/kg orally postpartum **ZDV** 4 mg/kg orally twice daily for first 6 weeks	**At 3 to 4 months (analysis excluded infants who were HIV positive at birth; postuterine infection was defined as negative at birth and then positive on day 10 or more)** 13.1% with ZDV *v* 7.9% with NVP Absolute numbers not reported RRR +40%, 95% CI –1% to +81%	**At 4 to 8 weeks** 13/533 (2.4%) with ZDV *v* 11/518 (2.1%) with NVP RR 1.15, 95% CI 0.52 to 2.54	NR
Prevention of postpartum MTCT: short-term antiretroviral regimens versus extended antiretroviral regimens					

Trial name; journal and year published	Study site and sample size	Intervention and comparison	Transmission rate Relative risk reduction (RRR)/efficacy	Infant mortality Relative risk (RR)	Still birth Relative risk (RR)
SWEN; Lancet 2008 [52]	Ethiopia, India, Uganda Antenatal and delivery facilities 2037 infants randomised who were HIV negative at birth (infants were deemed to be HIV positive at birth if they tested positive within 7 days of birth)	Single-dose NVP *v* 6 weeks' extended-dose NVP Breastfeeding **Single-dose NVP** *Mother* Single-dose NVP (200 mg) at onset of labour *Infant* Single-dose NVP after birth (2 mg/kg) **Extended-dose NVP** *Mother* Single-dose NVP (200 mg) at onset of labour *Infant* Single-dose NVP after birth (2 mg/kg) and NVP daily (5 mg) starting at day 8 through 6 weeks of life	**At 6 weeks** Kaplan–Meier analysis: 5.3% with single-dose NVP *v* 2.5% with extended-dose NVP RR (extended dose *v* single dose) 0.54, 95% CI 0.34 to 0.85 P = 0.009 **At 6 months** Kaplan–Meier analysis: 9.0% with single-dose NVP *v* 6.9% with extended-dose NVP RR (extended dose *v* single dose) 0.80, 95% CI 0.58 to 1.10 P = 0.16	**At 6 weeks** Kaplan–Meier analysis: 1.6% with single-dose NVP *v* 0.9% with extended-dose NVP RR (extended dose *v* single dose) 0.66, 95% CI 0.30 to 1.47 P = 0.31 **At 6 months** Kaplan–Meier analysis: 3.6% with single-dose NVP *v* 1.1% with extended-dose NVP RR (extended dose *v* single dose) 0.47, 95% CI 0.26 to 0.87 P = 0.02	NR
PEPI-Malawi; N Engl J Med 2008 [53]	Malawi 1 hospital and 5 affiliated health centres 3276 infants randomised; 3016 infants who were HIV negative at birth (tested negative for HIV within 48 hours of birth) included in analysis	Different regimens of extended prophylaxis with either NVP or ZDV *v* control in infants alone Breastfeeding (60% of women were exclusively breastfeeding at 6 months). All women received intrapartum single-dose nevirapine *Infant* **Extended prophylaxis with NVP** Single-dose NVP (2 mg/kg) plus 1 week of ZDV (4 mg/kg given twice daily for 1 week), plus daily NVP (2–4 mg/kg once daily) starting at day 8 and continuing until 14 weeks of age **Extended prophylaxis with NVP plus ZDV** Single-dose NVP (2 mg/kg) plus 1 week of ZDV (4 mg/kg given twice daily for 1 week), with daily NVP (2–4 mg/kg once daily) plus ZDV (8–18 mg/kg daily; various dosing schedules) starting at day 8 and continuing until 14 weeks of age **Control** Single-dose NVP (2 mg/kg) at birth plus 1 week of ZDV (4 mg/kg given twice daily)	**At 9 months** Kaplan–Meier analysis: 5.2% with extended NVP *v* 6.4% with extended NVP + ZDV *v* 10.6% with control Absolute numbers not reported **Extended NVP v control** P <0.001 **Extended NVP + ZDV *v* control A** P = 0.002 **Extended NVP *v* extended NVP + ZDV** Reported as not significant P value not reported	**At 9 months** 6.8% with extended NVP *v* 6.3% with extended NVP + ZDV *v* 8.9% with control **Extended NVP *v* control** Reported as not significant P value not reported **Extended NVP + ZDV *v* control A** Reported as not significant P value not reported **Extended NVP *v* extended NVP + ZDV** Reported as not significant P value not reported	NR

*efficacy as reported in the Cochrane review.
3TC, lamivudine; ART, antiretroviral therapy; d4T, stavudine; ddI, didanosine; iv, intravenously; MTCT, mother-to-child transmission; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NR, not reported; NS, not significant; NVP, nevirapine; Ref, reference; TDF/FTC, tenofovir and emtricitabine; ZDV, zidovudine.

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

Important outcomes	HIV transmission, infant 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) [31] [32] [33]	HIV transmission	Antiretrovirals *v* placebo in a breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of non-breastfeeding women in largest RCT (25% of women)
3 (2498) [31] [32] [33]	Infant mortality	Antiretrovirals *v* placebo in a breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	–1	0	–1	0	Low	Quality point deducted for methodological limitations (incomplete reporting of results). Directness point deducted for inclusion of non-breastfeeding women in largest RCT (25% of women)
1 (222) [34]	HIV transmission	Different durations of regimens using the same antiretrovirals *v* each other in a breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	0	0	0	0	High	
1 (222) [34]	Infant mortality	Different durations of regimens using the same antiretrovirals *v* each other in a breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	0	0	0	0	High	
4 (2346) [27] [28] [29] [30] [35] [36]	HIV transmission	Different antiretroviral regimens *v* each other in a breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	–1	0	–1	0	Low	Quality point deducted for methodological limitations (early termination of 1 RCT due to poor recruitment). Directness points deducted for use of a composite outcome in 1 RCT (includes mortality)
4 (2346) [27] [28] [29] [30] [35] [36]	Infant mortality	Different antiretroviral regimens *v* each other in a breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (early termination of 1 RCT due to poor recruitment).
3 (984) [38] [39] [40]	HIV transmission	Antiretrovirals *v* placebo in a non-breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	0	0	0	0	High	
2 (984) [33] [38] [39]	Infant mortality	Antiretrovirals *v* placebo in a non-breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results)
1 (1437) [41]	HIV transmission	Different durations of regimens using the same antiretrovirals *v* each other in a non-breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results)
1 (1109) [41]	Infant mortality	Different durations of regimens using the same antiretrovirals *v* each other in a non-breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results)

Important outcomes	HIV transmission, infant mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
4 (4165) [43] [44] [45] [42]	HIV transmission	Different antiretroviral regimens *v* each other in a non-breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (short follow-up in 1 study)
4 (4643) [43] [45] [42] [44]	Infant mortality	Different antiretroviral regimens *v* each other in a non-breastfeeding population (prevention of intrauterine and intrapartum MTCT)	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (short follow-up in 1 study and incomplete reporting of results)
3 (2632) [54] [55] [56]	HIV transmission	Different short-term antiretroviral regimens *v* each other (prevention of postpartum MTCT)	4	–1	–1	0	0	Low	Quality point deducted for methodological limitations (incomplete reporting of results in 1 RCT, subgroup analysis in 2 RCTs, and 1 RCT may have been underpowered to detect a clinically important difference for this outcome). Consistency point deducted for inconsistent results for the same regimen
3 (5053) [54] [55] [56]	Infant mortality	Different short-term antiretroviral regimens *v* each other (prevention of postpartum MTCT)	4	–1	–1	0	0	Low	Quality point deducted for methodological limitations (incomplete reporting of results in 1 RCT, and subgroup analysis in 2 RCTs). Consistency point deducted for inconsistent results for the same regimen
2 (5053) [52] [53]	HIV transmission	Short-term antiretroviral regimens *v* extended antiretroviral regimens (prevention of postpartum MTCT)	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results in 1 RCT, 1 RCT may have been underpowered to detect a clinically important difference for this outcome and there were differences among groups in usual care)
2 (5053) [52] [53]	Infant mortality	Short-term antiretroviral regimens *v* extended antiretroviral regimens (prevention of postpartum MTCT)	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results in 1 RCT, and differences among groups in usual care in 1 RCT)
1 (425) [5] [62]	HIV transmission	Formula feeding *v* breastfeeding alone	4	0	0	0	0	High	
1 (425) [5] [62]	HIV-free survival	Formula feeding *v* breastfeeding alone	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results)
1 (425) [5] [62]	Infant mortality	Formula feeding *v* breastfeeding alone	4	0	0	0	0	High	
1 (1200) [37]	HIV transmission	Formula feeding plus antiretrovirals *v* breastfeeding plus antiretrovirals for infants	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results and open-label RCT)
1 (1200) [37]	Infant mortality	Formula feeding plus antiretrovirals *v* breastfeeding plus antiretrovirals for infants	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results and open-label RCT)
1 (958) [63]	HIV transmission	Early cessation of breastfeeding *v* prolonged breastfeeding	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results and low adherence to recommended protocol in both groups)
1 (958) [63]	HIV-free survival	Early cessation of breastfeeding *v* prolonged breastfeeding	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (incomplete reporting of results and low adherence to recommended protocol in both groups)

Important outcomes	**HIV transmission, infant mortality, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (132) [63]	Infant mortality	Early cessation of breastfeeding *v* prolonged breastfeeding	4	–2	0	0	0	Low	Quality points deducted for sparse data and methodological limitations (incomplete reporting of results and for subgroup analysis, and low adherence to recommended protocol in both groups)
1 (436) [70]	HIV transmission	Elective caesarean section *v* vaginal delivery	4	0	0	–1	0	Moderate	Directness point deducted for differences in interventions between groups
1 (501) [71]	HIV transmission	HIV hyperimmune globulin *v* immunoglobulin without HIV antibody	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (1 RCT potentially underpowered to detect a clinically important difference)
2 (708) [72]	HIV transmission	Vaginal microbicides *v* no microbicides	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (randomisation flaws in included RCTs, and for 1 RCT being underpowered to detect a clinically meaningful difference)
2 (215) [72]	Infant mortality	Vaginal microbicides *v* no microbicides	4	–1	0	0	0	Moderate	Quality point deducted for methodological limitations (randomisation flaws in included RCTs, and for 1 RCT being underpowered to detect a clinically meaningful difference)
4 (6517) [74] [75]	HIV transmission	Vitamin A supplements *v* placebo/control	4	0	–1	0	0	Moderate	Consistency point deducted for heterogeneity among RCTs in meta-analysis
1 (3708) [75]	Infant mortality	Vitamin A supplements *v* placebo/control	4	–1	0	–1	0	Low	Quality point deducted for methodological limitations (incomplete reporting of data). Directness point deducted for using a composite outcome
1 (815) [80]	Infant mortality	Micronutrient supplements *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for methodological limitations (incomplete reporting and for short follow-up [6 months]). Directness point deducted for administration of maternal co-intervention throughout pregnancy (multivitamins)

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