Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection (Review)

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ABSTRACT

Background
Antiretroviral drugs (ARV) reduce viral replication and can reduce mother-to-child transmission of HIV either by lowing plasma viral load in pregnant women or through post-exposure prophylaxis in their newborns. In rich countries, highly active antiretroviral therapy (HAART) has reduced the vertical transmission rates to around 1-2%, but HAART is not yet widely available in low and middle income countries. In these countries, various simpler and less costly antiretroviral regimens have been offered to pregnant women or to their newborn babies, or to both.

Objectives
To determine whether, and to what extent, antiretroviral regimens aimed at decreasing the risk of mother-to-child transmission of HIV infection achieve a clinically useful decrease in transmission risk, and what effect these interventions have on maternal and infant mortality and morbidity.

Search strategy
We sought to identify all relevant studies regardless of language or publication status by searching the Cochrane HIV/AIDS Review Group Trials Register, The Cochrane Library, Medline, EMBASE and AIDSearch and relevant conference abstracts. We also contacted research organizations and experts in the field for unpublished and ongoing studies. The original review search strategy was updated in 2006.

Selection criteria
Randomised controlled trials of any antiretroviral regimen aimed at decreasing the risk of mother-to-child transmission of HIV infection compared with placebo or no treatment.

Data collection and analysis
Two authors independently selected relevant studies, extracted data and assessed trial quality. For the primary outcomes, we used survival analysis to estimate the probability of infants being infected with HIV (the observed proportion) at various specific time-points and calculated efficacy at a specific time as the relative reduction in the proportion infected. Efficacy, at a specific time, is defined as the preventive fraction in the exposed group compared to the reference group, which is the relative reduction in the proportion infected: 1-(Re/Rf). For those studies where efficacy and hence confidence intervals were not calculated, we calculated the approximate confidence intervals for the efficacy using recommended methods. For analysis of results that are not based on survival analyses we present the relative risk for each trial outcome based on the number randomised. No meta-analysis was conducted as no trial assessed the identical drug regimens.

Main results
Eighteen trials including 14,398 participants conducted in 16 countries were eligible for inclusion in the review. The first trial began in April 1991 and assessed zidovudine (ZDV) versus placebo and since then, the type, dosage and duration of drugs to be compared has been modified in each subsequent trial.

Antiretrovirals versus placebo

In breastfeeding populations, three trials found that:

ZDV given to mothers from 36 to 38 weeks gestation, during labour and for 7 days after delivery significantly reduced HIV infection at 4-8 weeks (Efficacy 32.00%; 95% CI 0.64 to 63.36), 3 to 4 months (Efficacy 34.00%; 95% CI 6.56 to 61.44), 6 months (Efficacy 35.00%; 95% CI 9.52 to 60.48), 12 months (Efficacy 34.00%; 95% CI 8.52 to 59.48) and 18 months (Efficacy 30.00%; 95% CI 2.56 to 57.44).

ZDV given to mothers from 36 weeks gestation and during labour significantly reduced HIV infection at 4 to 8 weeks (Efficacy 44.00%; 95% CI 8.72 to 79.28) and 3 to 4 months (Efficacy 37.00%; 95% CI 3.68 to 70.32) but not at birth.

ZDV plus lamivudine (3TC) given to mothers from 36 weeks gestation, during labour and for 7 days after delivery and to babies for the first 7 days of life (PETRA 'regimen A') significantly reduced HIV infection (Efficacy 63.00%; 95% CI 41.44 to 84.56) and a combined endpoint of HIV infection or death (Efficacy 61.00%; 95% CI 41.40 to 80.60) at 4 to 8 weeks but these effects were not sustained at 18 months.

ZDV plus 3TC given to mothers from the start of labour until 7 days after delivery and to babies for the first 7 days of life (PETRA 'regimen B') significantly reduced HIV infection (Efficacy 42.00%; 95% CI 12.60 to 71.40) and HIV infection or death at 4 to 8 weeks (Efficacy 36.00%; 95% CI 8.56 to 63.44) but the effects were not sustained at 18 months.

ZDV plus 3TC given to mothers during labour only (PETRA 'regimen C') with no treatment to babies did not reduce the risk of HIV infection at either 4 to 8 weeks or 18 months.

In non-breastfeeding populations, three trials found that:

ZDV given to mothers from 14 to 34 weeks gestation and during labour and to babies for the first 6 weeks of life significantly reduced HIV infection in babies at 18 months (Efficacy 66.00%; 95% CI 34.64 to 97.36).

ZDV given to mothers from 36 weeks gestation and during labour with no treatment to babies ('Thai-CDC regimen') significantly reduced HIV infection at 4 to 8 weeks (Efficacy 50.00%; 95% CI 12.76 to 87.24) but not at birth

ZDV given to mothers from 38 weeks gestation and during labour with no treatment to babies did not influence HIV transmission at 6 months.

Longer versus shorter regimens using the same antiretrovirals

One trial in a breastfeeding population found that:

ZDV given to mothers during labour and to their babies for the first 3 days of life compared with ZDV given to mothers from 36 weeks and during labour (similar to 'Thai-CDC') resulted in HIV infection rates that were not significantly different at birth, 4-8 weeks, 3 to 4 months, 6 months and 12 months.

Three trials in non-breastfeeding populations found that:

ZDV given to mothers from 28 weeks gestation during labour and to infants for the first 3 days after birth compared with ZDV given to mothers from 35 weeks gestation through labour and to infants from birth to 6 weeks significantly reduced HIV infection rate at 6 months (Efficacy 45.00%; 95% CI 1.88 to 88.12) but compared with the same regimen ZDV given to mothers from 28 weeks gestation through labour and to infants from birth to 6 weeks did not result in a statistically significant difference in HIV infection at 6 months. ZDV given to mothers from 35 weeks gestation during labour and to infants for the first 3 days after birth was considered ineffective for reducing transmission rates and this regimen was discontinued.

An antenatal/intrapartum course of ZDV used for a median of 76 days compared with an antenatal/intrapartum ZDV regimen used for a median 28 days with no treatment to babies in either group did not result in HIV infection rates that were significantly different at birth and at 3 to 4 months.

In a programme where mothers were routinely receiving ZDV in the third trimester of pregnancy and babies were receiving one week of ZDV therapy, a single dose of nevirapine (NVP) given to mothers in labour and to their babies soon after birth compared with a single dose of NVP given to mothers only resulted in HIV infection rates that were not significantly different at birth and 6 months. However the reduction in risk of HIV infection or death at 6 months was marginally significant (Efficacy 45.00%; 95% CI -4.00 to 94.00).

Antiretroviral regimens using different drugs and durations of treatment

In breastfeeding populations, three trials found that:

A single dose of NVP given to mothers at the onset of labour plus a single dose of NVP given to their babies immediately after birth ('HIVNET 012 regimen') compared with ZDV given to mothers during labour and to their babies for a week after birth resulted in lower HIV infection rates at 4-8 weeks (Efficacy 41.00%; 95% CI 11.60 to 70.40), 3-4 months (Efficacy 39.00%; 95% CI 11.56 to 66.44), 12 months (Efficacy 36.00%; 95% CI 8.56 to 63.44) and 18 months (Efficacy 39.00%; 95% CI 13.52 to 64.48). In addition, the NVP regimen significantly reduced the risk of HIV infection or death at 4-8 weeks (Efficacy 42.00%; 95% CI 14.56 to 69.44), 3 to 4 months (Efficacy 40.00%; 95% CI 14.52 to 65.48), 12 months (Efficacy 32.00%; 95% CI 8.48 to 55.52) and 18 months (Efficacy 33.00%; 95% CI 9.48 to 56.52).

The 'HIVNET 012 regimen' plus ZDV given to babies for 1 week after birth compared with the 'HIVNET 012 regimen' alone did not result in a statistically significant difference in HIV infection at 4 to 8 weeks.

A single dose of NVP given to babies immediately after birth plus ZDV given to babies for 1 week after birth compared with a single dose of NVP given to babies only significantly reduced the HIV infection rate at 4 to 8 weeks (Efficacy 37.00%; 95% CI 3.68 to 70.32).

Five trials in non-breastfeeding populations found that:

In a population in which mothers were receiving 'standard' ARV for HIV infection a single dose of NVP given to mothers in labour plus a single dose of NVP given to babies immediately after birth ('HIVNET 012 regimen') compared with placebo did not result in a statistically significant difference in HIV infection rates at birth and at 4 to 8 weeks.

The 'Thai CDC regimen' compared with the 'HIVNET 012 regimen' did not result in a significant difference in HIV infection at 4 to 8 weeks.

A single dose of NVP given to babies immediately after birth compared to ZDV given to babies for the first 6 weeks of life did not result in a significant difference in HIV infection rates at 4-8 weeks and 3 to 4 months.

ZDV plus 3TC given to mothers in labour and for a week after delivery and to their infants for a week after birth (similar to 'PETRA regimen B') compared with NVP given to mothers in labour and immediately after delivery plus a single dose of NVP to their babies immediately after birth (similar to 'HIVNET 012 regimen') did not result in a significant difference in the HIV infection rate at 4 to 8 weeks.

An evaluation of various ARV drugs given to mothers from 34 to 36 weeks and during labour with the same drugs given to their babies for 6 weeks after birth: stavudine (d4T) versus ZDV, didanosine (ddI) versus ZDV and d4T plus ddI versus ZDV did not result in statistically important differences in HIV infection rates at birth, 4 to 8 weeks, 3 to 4 months and 6 months.

Adverse effects

The incidence of serious or life threatening events was not significantly different in any of the trials included in this review.

Authors' conclusions

Short courses of antiretroviral drugs are effective for reducing mother-to-child transmission of HIV and are not associated with any safety concerns in the short-term. A combination of ZDV and 3TC given to mothers in the antenatal, intrapartum and postpartum periods and to babies for a week after delivery or a single dose of NVP given to mothers in labour and babies immediately after birth may be most effective. Where HIV infected women present late for delivery, post-exposure prophylaxis with a single dose of NVP immediately after birth plus ZDV for the first 6 weeks of life is beneficial. The long term implications of the emergence of resistant mutations following the use of these regimens require further study

PLAIN LANGUAGE SUMMARY

Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Millions of children worldwide acquire HIV/AIDS as a result of mother-to-child transmission (MTCT) during either pregnancy or breastfeeding. This is the primary means of infection for children under the age of 15 years. Researchers theorized that a course of antiretroviral drugs (ARV) given to pregnant women and their newborn babies could reduce the risk of mother-to-child transmission.

At the end of 2005, 2.3 million children under the age of 15 years were estimated to be living with HIV/AIDS. The majority of these children acquired their infections as a result of mother-to-child transmission during pregnancy, labor, or breastfeeding. Antiretroviral drugs reduce the viral load and can reduce the rates of mother-to-child transmission. The objective of this review is to determine whether a regimen of antiretroviral drugs would lead to a significant reduction in HIV transmission and maternal and infant mortality and morbidity.

The eighteen trials found eligible for inclusion in this review were conducted in 16 countries and included 14,398 participants. The trials compared the use of antiretrovirals versus placebo, longer regimens versus shorter regimens using the same antiretrovirals, and antiretroviral regimens using different drugs and different durations of treatment. This review of trials found that short courses of certain antiretroviral drugs are effective in reducing mother-to-child transmission of HIV, and are not associated with any safety concerns in the short term.

BACKGROUND

At the end of 2005, 2.3 million children under the age of 15 years were estimated to be living with HIV/AIDS, with 80% of these resident in sub-Saharan Africa (UNAIDS/WHO 2005). In 2004 alone an estimated 700,000 children under 15 years of age were newly infected with HIV, and more than three quarters of these infections occurred in sub-Saharan Africa (UNAIDS/WHO 2005). The vast majority of these children will have acquired their infection as a result of mother-to-child transmission (MTCT) during pregnancy, in the intrapartum period or postnatally through breast feeding. Based on a review of 13 cohort studies the risk of vertical transmission of HIV without antiretroviral treatment was estimated to be about 15-20% in Europe, 15-30% in the USA, and 25-35% in Africa (Working Group 1995).

Maternal viral load (the amount of HIV RNA in the plasma) is a strong independent determinant of the risk of MTCT (John 1996; Khouri 1995; Mofenson 1995). Other risk factors for transmission include breastfeeding, sexually transmitted diseases, chorioamnionitis, prolonged rupture of membranes, vaginal mode of delivery, low CD4 count, advanced maternal HIV disease, obstetric events increasing bleeding (episiotomy, perineal laceration, and intrapartum haemorrhage), young maternal age, and history of stillbirth (Dunn 1992; European Collab 1992; Jamieson 2003; Minkoff 1995; Miotti 1999; Mofenson 1995; Nair 1993).

In African countries, HIV infection is contributing substantially to infant and child mortality and this effect is reversing gains in child survival. A recent study reported that, in children under five years of age living in sub-Saharan Africa, HIV accounted for 2% of deaths in 1990 increasing to almost 8% in 1999 (Walker 2002). Five countries (Botswana, Namibia, Swaziland, Zambia, and Zimbabwe) had rates of HIV-attributable mortality in excess of 30/1000 in children under the age of five years. Interventions aimed at reducing the risk of MTCT are therefore a priority if childhood mortality is to be reduced. As the greatest burden of disease due to HIV infection in pregnancy is in those parts of the world least able to afford expensive and complex interventions, it is essential that these interventions be simple and affordable.

Antiretroviral drugs can reduce mother-to-child transmission of HIV in one of more the following ways 1) by reducing viral replication and thus lowering plasma viral load in pregnant women; 2) through pre-exposure prophylaxis of babies by crossing the placenta; and 3) through post-exposure prophylaxis of babies after delivery. In developed countries, highly active antiretroviral therapy (HAART) has reduced the vertical transmission rates to around 1-2% but HAART is not yet widely available in low and middle income countries. In these countries, various simpler and less costly ARV regimens have been offered to pregnant women and/or their newborn babies.

Antiretroviral drugs can be grouped into the following classes:

1. Nucleoside analogue reverse transcriptase inhibitors:
This class of drugs includes zidovudine (ZDV, previously known as AZT), lamivudine (3TC), didanosine (ddI), stavudine (d4T) and abacavir (ABC).

2. Non-nucleoside analogue reverse transcriptase inhibitors.
This class of drugs includes nevirapine (NVP), delavirdine and efavirenz.

3. Protease inhibitors.
This class of drugs includes indinavir, ritonavir, nelfinavir and saquinavir.

Some of the more commonly used antiretroviral drugs in pregnancy are:
Zidovudine
ZDV was the first antiretroviral drug to be approved by the US Food and Drug Administration (FDA) in March 1987. Like all nucleoside analogues, it inhibits HIV replication by inhibiting the enzyme reverse transcriptase required for transcription of viral RNA to DNA prior to insertion into the host cell genome. It is the drug, which has been most extensively used in pregnancy.

Nevirapine
NVP is rapidly absorbed when given orally and has potent antiretroviral activity. In addition, it has a very long half life (Mirochnick 1998; Musoke 1999). Prolonged use of NVP as

monotherapy leads to rapid development of resistant virus, which limits its usefulness when treating HIV infection in the long term.

Combination antiretroviral therapy
Over the past five years, trials in adults have shown that combination therapy is associated with a prolonged suppression of viral replication with marked reductions in viral load as well as a delay in the emergence of viral resistance. These effects seem to be translated into clinical benefit (Hammer 1997; Morcroft 2000). As higher maternal viral loads are associated with a greater risk of mother-to-child transmission of HIV infection, any intervention that substantially reduces viral load may decrease the likelihood of mother-to-child transmission. Trials of combination antiretroviral therapy in pregnancy are necessary to weigh these potential benefits against the potential risks of exposing large numbers of uninfected fetuses to drugs of unknown toxicity or teratogenicity.

In the light of the above, a systematic review of all currently trialed interventions for preventing MTCT will provide evidence to assist policy-makers, clinicians and consumers in choosing the most effective drug regimen. Additionally such a review will help identify the gaps in the research evidence and provide evidence-based direction for future trials.

OBJECTIVES

To determine whether, and to what extent, antiretroviral therapies aimed at decreasing the risk of mother-to-child transmission of HIV infection achieve a clinically useful decrease in transmission risk, and what effect these interventions have on maternal and infant mortality and morbidity.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials of any antiretroviral regimen aimed at decreasing the risk of mother-to-child transmission of HIV infection compared with placebo or no treatment.

Randomised controlled trials comparing two or more antiretroviral regimens aimed at decreasing the risk of mother-to-child transmission of HIV infection.

Trials designed only to address postnatal breast milk transmission have not been included in this review, but will be included in an updated review.

Types of participants

Pregnant women with HIV infection or infants born to mothers with HIV infection.

Types of intervention

Any antiretroviral regimen with the specific aim of decreasing the risk of mother-to-child transmission of HIV infection.

Types of outcome measures

PRIMARY OUTCOMES

1. HIV infection status at birth, at 2 weeks, 4 to 8 weeks, 3 to 4 months, and at 6, 12 and 18 months;
2. HIV or death at 2 weeks, 4 to 8 weeks, 3 to 4 months, and at 6, 12 and 18 months.

SECONDARY OUTCOMES
1. Infant death at 2 weeks, 4 to 8 weeks, 3 to 4 months, and at 6, 12 and 18 months.
2. Stillbirth;
3. Low birth weight (less than 2500g);
4. Premature delivery (as defined by the authors).

ADVERSE EVENTS
Severe adverse events are reported for mothers and infants. If they are classified according to grade 1 to 4 of the Adverse Event Toxicity Scale, we report only grade 3 and 4 events. Using this scale, grade 1 and 2 denote mild to moderate symptoms, grade 3 denote serious symptoms and grade 4 denote life-threatening events requiring significant clinical intervention.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

See: HIV/AIDS Collaborative Review Group search strategy.

The original review, published in 2002, used a search strategy developed for the Pregnancy and Childbirth Group as a whole. Relevant trials were identified in the Group's Specialized Register of Controlled Trials. (See the Pregnancy and Childbirth Review Group's details for more information.) In addition, the Cochrane Controlled Trials Register was searched with each new edition of the Cochrane Library. Conference abstracts from the International AIDS Conferences and Conference on Retroviruses and Opportunistic Infections were also searched.

For this update of the review, the search strategy was further refined with the assistance of the HIV/AIDS Review Group Trials Search Co-ordinator. We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). Full details of the Cochrane HIV/AIDS Review Group methods and the journals hand-searched are published in the section on Collaborative Review Groups in the Cochrane Library. We used the RCT search strategy developed by The Cochrane Collaboration and detailed in the Cochrane Reviewers' Handbook in combination

with terms specific to mother-to-child transmission. We searched the following electronic databases:

(1) Medline (1966 to date) via PubMed on 17 February 2004 and updated on 31 January 2005 and again on 9 February 2006 using the strategy documented in Table 01.

The searches conducted in 2005 and 2006 yielded 265 records in total of which we selected 29 for full article retrieval. (The search in 2004 yielded 276 records but no record was kept of the number of full articles retrieved for that search.)

(2) EMBASE (2000 to date) on 5 April 2004 and updated again on 31 January 2005 and 9 February 2006 using the PUBMED strategy modified for EMBASE documented in Table 02.

The searches conducted in 2005 and 2006 yielded 39 records in total of which we selected 15 for full article retrieval. (The search in 2004 yielded 116 records but no record was kept of the number of full articles retrieved.)

(3) AIDSearch (1995 to date) on 31 January 2005 and again on 9 February 2006. The database includes coverage of the following conferences:
- International AIDS conference (1985-2004)
- Conference on Retroviruses and Opportunistic Infections (1986-2004)
- The British HIV Association conference (1997-2003)
- International Congress on Drug Therapy in HIV infection (1994-2002)

We limited our search to 2004 onwards, which yielded 28 records in total of which we selected eight for full article retrieval. See Table 03 for the full search strategy.

(4) The Cochrane Library Controlled Trials Register on 7 April 2004 and again on 31 January 2005 and 9 February 2006. The searches conducted in 2005 and 2006 yielded 12 records in total of which we selected four for full article retrieval. (The search in 2004 yielded 61 records but no record was kept of the number of full articles retrieved.) See Table 04 for search strategy.

There was some overlap between the references retrieved in each database. We also checked the reference lists of all the articles retrieved by the search strategy for relevant studies and searched a database of HIV/AIDS RCTs conducted in Africa up until 2004 (Siegfried 2005). Finally, we contacted research organizations and experts in the field for unpublished and ongoing studies and have included these as studies for future assessment.

METHODS OF THE REVIEW

JV and NS independently conducted the selection of potentially relevant studies by scanning the titles, abstracts, and descriptor terms of all downloaded material from the electronic searches. Irrelevant reports were discarded, and the full article was obtained for all potentially relevant or uncertain reports. Any disagreements were resolved by discussion.

(1) Selection of studies:

JV and NS independently applied the inclusion criteria, using an eligibility form specific to this review. Studies were reviewed for relevance, based on study design, types of participants, exposures and outcome measures. Finally, where resolution was not possible because further information was required, the study was allocated to the list of those awaiting assessment. Attempts to contact authors to provide further clarification of data are ongoing.

(2) Data extraction:

JV and NS independently extracted trial details using a standardised data extraction form. The following characteristics were extracted from each included study:

Administrative details:
Identification; author(s); published or unpublished; year of publication; number of studies included in paper; month and year in which enrolment into the trial commenced; details of other relevant papers cited.

Details of study:
Study design; type, duration and completeness of follow-up; country and location of the study.

Characteristics of participants:
Inclusion and exclusion criteria including diagnostic criteria for HIV in mothers and infants; mode of feeding (breastfeeding, formula-feeding or mixed).

Details of intervention:
Types and doses of drugs used; duration of therapy; details of serious adverse events

Outcomes:
LvdM and NS independently extracted the numerical data using a standardised spreadsheet for each trial. Numerical data included the raw numbers and the reported survival analysis estimates when provided for the outcomes described under the Types of Outcomes section above. Where numbers for an outcome differed in different reports of the same trial we used the numbers reported in the most recently published trial report. Any disagreements were resolved by consulting JV.

(3) Quality assessment:

Trial quality was assessed by evaluating the method used for generating the randomisation sequence, the adequacy of allocation concealment, the adequacy of blinding of participants, providers and assessors, and the differential loss-to-follow-up in the comparison groups. We did not attempt to quantify trial quality, but described it in full.

(4) Data synthesis:

The primary outcome is the estimated transmission rate of HIV (the observed proportion) at various specific time-points. This is best accomplished using survival analysis methods because it incorporates all available information including the time until infants are diagnosed with HIV infection, or the time until they are tested and are free from infection, or the time until they are lost-to-follow-up (Ghent 2001). We therefore chose where possible to analyse the reported estimates of the transmission rates. Where these were not reported, we estimated them directly using the published data.

Several studies reported the efficacy of the intervention compared to the control. Efficacy, at a specific time, is defined as the preventive fraction in the exposed group compared to the reference group (Ghent 2001), which is the relative reduction in the proportion infected: 1-(Re/Rf). Here Re is the estimated cumulative rate of transmission in the experimental group and Rf is the estimated cumulative rate of transmission in the reference group. We reported the efficacies of the studies up to the specified time-points. For those studies where efficacy and hence confidence intervals were not reported, we calculated the confidence intervals for the efficacy using the recommended methods (Wilson and Newcombe described in Altman 2005).

Three trials only compared interventions given to babies (Taha 2003; Taha 2004; Gray 2005). This means transmission efficacy at birth is not relevant for these trials.

We report the outcomes using the efficacy estimates described above for each trial. For analysis of results which are not based on survival analyses e.g. stillbirths, we present the relative risk for each trial outcome based on the number randomized, not the number analyzed.

DESCRIPTION OF STUDIES

We identified 18 trials that met our inclusion criteria, an additional 10 trials since the review was published in 2002. Overall the 18 trials included 14,398 participants with a median trial sample size of 795 ranging from 50 (Bhoopat 2005) to 1,797 participants (PETRA). Seventeen trials randomized mothers and followed up their infants, and one trial (Taha 2004) randomised infants.

Most trials (N=14) were conducted in a single country, all in poor regions of the world: Thailand (N=5), South Africa (N=3), Malawi (N=2), Cote d'Ivoire (N=1), Kenya (N=1), Uganda (N=1), and Zimbabwe (N=1). See Figure 02 and Figure 03. Of the four multinational trials, two were conducted across countries in Africa: the DITRAME trial was conducted in Cote d'Ivoire and in Burkina Faso; and the PETRA trial was conducted in South Africa, Tanzania and Uganda. Two multinational, multicentre trials were conducted in rich countries: the PACTG 076 trial in the USA and France, and the PACTG 316 in the USA, Puerto Rico, Europe, Brazil and the Bahamas. The locations of the multinational trials are shown in Figure 04 (best viewed in colour if printed).

Seven trials, all conducted in Africa, included mothers who were breastfeeding (DITRAME; HIVNET 012; PETRA; RETRO-CI; Taha 2003; Taha 2004; Thistle 2004). Eight trials were conducted in non-breast-feeding populations: all of the trials conducted in Thailand (N=5) included mothers willing to formula feed (Bhoopat 2005; Limpongsanurak 2001; PHPT-1; PHPT-2; Thai-CDC;) as did the two multinational, multicentre trials (PACTG 076; PACTG 316) and the Gray 2006 trial conducted in Soweto, South Africa. In the SAINT study conducted in South Africa, 46% of the 1,319 included mothers reported breastfeeding at birth reducing to 32% at 8 weeks. In the Kiarie 2003 study conducted in Kenya, 66% of the 188 included mothers reported breastfeeding at 1 week. The mode of feeding at birth was reported to be 84% exclusive formula feeding, 15% breast milk exposure and 1% mixed feeding in the Gray 2005 trial.

The first trial to assess antiretrovirals for reducing MTCT was PACTG 076, which began enrolling participants in April 1991. The trial was conducted in 59 centres in the USA and France and compared 198 mothers receiving a dose of 100 mg of ZDV five times daily from 14 to 34 weeks gestation until onset of labour with 204 mothers receiving a placebo. During labour those mothers randomized to the treatment group received a 2 mg/kg loading dose of ZDV intravenously followed by a dose of 1 mg/kg/hr until delivery and their infants received ZDV syrup at a dose of 2 mg/kg six hourly for six weeks after birth. Infants in the control group received a placebo. This trial was stopped during the first interim analysis in December 1993, as the difference in favour of ZDV was statistically significant.

Since then, the type, dosage and period of drugs to be compared has been modified in each subsequent trial. No two trials in this review compare identical interventions (see Table of Included Studies for more detail). In addition, the diagnostic tests used to diagnose HIV infection in both mother and infants differ between trials and over time, as do the criteria for the diagnosis of HIV infection and the time-points at which blood samples were taken (see Figure 01). Trials in the breastfeeding populations continue for a longer period than those in non-breastfeeding in order to assess any additional benefit of ARVs in reducing breast-milk transmission.

METHODOLOGICAL QUALITY

GENERATION OF RANDOM SEQUENCE

Eight trials reported adequate generation of the random sequence (DITRAME; Gray 2005; HIVNET 012; SAINT; Taha 2003; Taha 2004; Thai-CDC; Thistle 2004) and the other ten trials either did not report how this was done or the report was unclear. All eight trials reporting adequate generation used computerised methods for generating the sequence.

ALLOCATION CONCEALMENT

Eleven trials reported adequate allocation concealment (DITRAME; Gray 2005; HIVNET 012; PETRA; PHPT-1;PHPT-2; RETRO-CI; Taha 2003; Taha 2004; Thai-CDC; Thistle 2004), and seven trials failed to report on allocation concealment. Of those trials with adequate allocation concealment, one trial reported providing the allocation schedule in ordered opaque envelopes (Thistle 2004) and the remaining 10 trials reported concealing allocation by providing sequentially numbered sealed treatment packs prepared off-site.

MASKING OF PROVIDERS; PARTICIPANTS AND ASSESSORS

Clear information on who was masked was reported in seven trials; three of these clearly reported masking the providers, participants and assessors (Limpongsanurak 2001; PHPT-2; Thai-CDC), and four of these clearly reported on masking the assessor but not the provider or participant (HIVNET 012; SAINT; Taha 2003; Taha 2004). The remaining 11 trials did not clearly report masking at every stage: six of these trials clearly reported masking at the provider and participant stage but were unclear regarding the masking of the assessor (DITRAME; PACTG 316; PETRA; PHPT-1; RETRO-CI; Thistle 2004); three trials clearly reported that the provider and participant were not masked but were unclear about the masking of the assessor (Gray 2005; Gray 2006; Kiarie 2003); one trial clearly reported masking the provider but was unclear about the other stages (PACTG 076); and one trial report was unclear about every stage of masking (Bhoopat 2005).

ATTRITION

In order to standardise the reporting of attrition in each trial we calculated a percentage of the number of participants randomized for overall exclusions which included protocol violations after randomisation (even if these were before birth of the baby); termination of treatment (e.g. because of adverse events) and those who were lost-to-follow-up. However, because these figures were variably reported across trials, the attrition rate we report should be treated with caution.

Overall, the median attrition rate was 14% ranging from 0% in the Bhoopat 2005 trial to 31.7% overall in the Gray 2005 trial. Seven trials reported attrition greater than 20% and this could be an important source of bias in those trials with smaller sample sizes (see Table of Included Studies). The use of survival analysis in most of these trials would however, reduce the impact of a high attrition rate as it allows for censoring of participants.

RESULTS

We have grouped the trials according to type of comparison e.g. antiretrovirals vs placebo, and within each group stratify according to whether the study was conducted in a breastfeeding population or not. Breastfeeding is defined as greater than 90% of included women breastfeeding their infants at birth. Within strata the results are provided for each trial with the latter ordered chronologically on the date of the start of the trial rather than the date when the report was published.

ANTIRETROVIRALS VS PLACEBO (See comparison 01)

BREASTFEEDING

Three trials assessed this comparison (DITRAME; RETRO-CI; PETRA).

DITRAME

ZDV given to mothers from 36 to 38 weeks gestation, during labour and for 7 days after delivery with no treatment to infants significantly reduced HIV infection at 4-8 weeks (Efficacy 32.00; 95% CI 0.64 to 63.36), 3 to 4 months (Efficacy 34.00; 95% CI 6.56 to 61.44), 6 months (Efficacy 35.00%; 95% CI 9.52 to 60.48), 12 months (Efficacy 34.00%; 95% CI 8.52 to 59.48) and 18 months (Efficacy 30.00%; 95% CI 2.56 to 57.44). The treatment did not influence risk of infant death in the first week of life (RR 2.03; 95% CI 0.51 to 8.00), in the first 4 to 8 weeks (RR 1.77; 95% CI 0.53 to 5.97), in the first 3 to 4 months (RR 0.74; 95% CI 0.35 to 1.58), in the first 6 months (RR 0.62; 95% CI 0.35 to 1.09), in the first 12 months (RR 0.75; 95% CI 0.48 to 1.17) and in the first 18 months (RR 0.80; 95% CI 0.53 to 1.21). The study found a statistically significant reduction in the rate of premature delivery (RR 0.14; 95% CI 0.03 to 0.58 but no difference in the risk of low birthweight (RR 0.92; 95% CI 0.57 to 1.47). The difference in the risk of stillbirth was not statistically significant (RR 0.14; 95% CI 0.02 to 1.17).

Adverse events

Mothers: There was no significant difference in the frequency of death by 6 weeks (1 with ZDV vs 2 with placebo; p=1.0), severe anaemia at day 8 or 45 days postpartum (11 with ZDV vs 8 with placebo; p=0.47) and severe neutropenia at day 8 or 45 (1 with ZDV vs 1 with placebo; p=0.99). Both types of blood disorders were transient.

Infants: There was no significant difference in the frequency of severe anaemia (10 with ZDV vs 12 with placebo; p=0.67) and severe neutropenia (1 with ZDV vs 4 with placebo; p=0.37); both types of disorder disappeared by 45 days.

RETRO-CI

ZDV given to mothers from 36 weeks gestation and in labour but not to babies significantly reduced HIV infection at 4 to 8 weeks (Efficacy 44.00%; 95% CI 8.72 to 79.28) and 3 to 4 months (Efficacy 37.00%; 95% CI 3.68 to 70.32) but not at birth (Efficacy -14.00%; 95% CI -162.96 to 134.96). Treatment also reduced the risk of infant death in the first week of life (RR 0.13; 95% CI 0.02 to 0.99) and during the first 3 to 4 months of life (RR 0.15; 95% CI 0.05 to 0.49) but not the risk of stillbirth (RR 3.50 95% CI 0.74 to 16.55)

Adverse events

Mothers: There was no significant difference in the frequency of postpartum death (1 with ZDV vs 5 with placebo; p=0.21), severe clinical disorder (1 reported case each of painful joints and vomiting with ZDV and 0 with placebo; p=0.25) and severe laboratory abnormality (mostly low haemoglobin) (7 with ZDV vs 9 with placebo; p=0.80).
Infants: There was no significant difference in the frequency of congenital abnormality (2 with ZDV vs 6 with placebo; p=0.28) and severe laboratory abnormality (mostly low haemoglobin) (8 with ZDV vs 17 with placebo; p=0.09); low haemoglobin was transient.

PETRA
In this study, combinations of ZDV and 3TC delivered in three different arms were compared to a placebo arm. We present the results for each of the arms compared with the placebo arm (see Table of Included Studies for full details of each arm)

PETRA a
Regimen A : ZDV plus 3TC given to mothers from 36 weeks gestation through labour and continued for 7 days after delivery and to babies for the first 7 days of life significantly reduced HIV infection at 4 to 8 weeks (Efficacy 63.00%; 95% CI 41.44 to 84.56) but not at 18 months (Efficacy 33.00%; 95% CI -12.08 to 78.08). The incidence of a combined endpoint of HIV infection or death was also significantly reduced (Efficacy 61.00%; 95% CI 41.40 to 80.60) at 4 to 8 weeks but not at 18 months (Efficacy 26.00%; 95% CI -13.20 to 65.20). There was no statistically significant difference in infant mortality in the first 4 to 8 weeks (RR 0.35; 95% CI 0.11 to 1.14) or in the first 18 months (RR 0.76; 95% CI 0.50 to 1.14) and no difference in the rates of stillbirths (RR 0.40 95% CI 0.07 to 2.15)

PETRA b
Regimen B: ZDV plus 3TC given to mothers from the start of labour until 7 days after delivery and to babies for the first 7 days of life significantly reduced HIV infection at 4 to 8 weeks (Efficacy 42.00%; 95% CI 12.60 to 71.40) but not at 18 months (Efficacy 18.00%; 95% CI -27.08 to 63.08). The risk of HIV infection or death was significantly reduced at 4 to 8 weeks (Efficacy 36.00%; 95% CI 8.56 to 63.44) but not at 18 months (Efficacy 7.00%; 95% CI -40.04 to 54.04). There was no statistically significant difference in infant mortality in the first 4 to 8 weeks (RR 0.71; 95% CI 0.28 to 1.81) or in the first 18 months (RR 1.05; 95% CI 0.73 to 1.51) and no difference in stillbirth rates (RR 1.19 95% CI 0.34 to 4.20)

PETRA c
Regimen C: ZDV plus 3TC given to mothers during labour only with no treatment to babies did not reduce HIV infection at either 4 to 8 weeks (Efficacy 7.00%; 95% CI -32.20 to 46.20) or 18 months (Efficacy 10.00%; 95% CI -40.96 to 60.96). There was also no difference in the combined outcome of HIV infection or death at 4 to 8 weeks (Efficacy 3.00%; 95% CI -32.28 to 38.28) and at 18 months (Efficacy 2.00%; 95% CI -45.04 to 49.04). Infant mortality was similar in the comparison groups in the first 4 to 8 weeks (RR 0.98; 95% CI 0.41 to 2.34) and in the first 18 months (RR 0.96; 95% CI 0.66 to 1.39) and no significant difference in the risk of stillbirth (RR 0.80 95% CI 0.20 to 3.18)

Adverse events
Mothers: There was no significant difference in the frequency of grade 3 and 4 laboratory events (with respect to haemoglobin, leucocytes, lymphocytes, thrombocytes, creatinine, or transaminase levels) before week 6 (32 with regimen A, 22 with regimen B, 26 with regimen C, and 29 with placebo; p=0.47).
Infants: There was no significant difference in the frequency of grade 3 and 4 laboratory events (20 with regimen A, 18 with regimen B, 24 with regimen C, and 28 with placebo; p=96), neurological events up to 18 months (9 with regimen A, 13 with regimen B, 15 with regimen C, and 10 with placebo; p=0.61) and congenital abnormalities 28 with regimen A, 27 with regimen B, 24 with regimen C, and 28 with placebo; p=0.89)

NON BREASTFEEDING

Three trials assessed this comparison (PACTG 076; Limpongsanurak 2001; Thai-CDC)

PACTG 076
ZDV administered to mothers from 14 to 34 weeks gestation and continued through labour and to babies for the first 6 weeks of life significantly reduced HIV infection in babies at 18 months (Efficacy 66.00%; 95% CI 34.64 to 97.36). The treatment did not reduce the risk of infant death in the first 18 months (RR 1.33; 95% CI 0.30 to 5.87) or the rates of premature delivery (R1.23; 95 CI 0.60 to 2.49) and low birth weight (RR 0.75; 95% CI 0.48 to 1.19). No difference in stillbirth rates was found (RR 0.33; 95% CI 0.01 to 8.11)

Adverse events
Mothers: There were no deaths in either group. The rates of severe haematological toxicity (18 with ZDV and 16 with placebo; p=0.82) and severe chemistry toxicity (7 with ZDV and 2 with placebo; p=0.09) were not significantly different.
Infants: The frequency of anaemia (Hb<9.0g/dL) in the first 6 weeks of life was higher in the ZDV group (44 with ZDV vs 24 with placebo; p=0.001); of these 4 infants in each group had a Hb <7.0 g/dL. The anaemia resolved by 12 weeks of a

Limpongsanurak 2001
ZDV given to mothers from 38 weeks gestation and in labour but not to their babies did not influence HIV transmission at 6 months (Efficacy 9.00%; 95% CI -26.28 to 44.28). There was also no significant difference in the rate of stillbirths between the two groups (RR 3.07; 95% CI 0.13 to 74.28).

Adverse events
Not reported

Thai-CDC

ZDV given to mothers from 36 weeks gestation and in labour with no treatment to babies significantly reduced HIV infection at 4 to 8 weeks (Efficacy 50.00%; 95% CI 12.76 to 87.24) but not at birth (Efficacy 30.00, 95% CI -42.52 to 102.52). There was no significant reduction in the risk of stillbirth (RR 3.02; 95% CI 0.12 to 73.57), low birth weight (RR 0.61; 95% CI 0.30 to 1.27) or infant death in the first 4-8 weeks of life (RR 0.50; 95% CI 0.05 to 5.50).

Adverse events
Mothers: There were no deaths in either group. There was no significant difference in the frequency of severe postpartum anaemia (haematocrit <24%) (13 with ZDV vs 10 with placebo; p not reported).
Infants: There was no significant difference in the risk of grade 3 haematological effects: haematocrit<36% at birth (2 with ZDV and 1 with placebo) or <21% at 2 months (0 with ZDV and 1 with placebo; p values not reported). The number of congenital abnormalities was similar (4 with ZDV vs 3 with placebo; p not reported). During 18 months follow up no statistically significant differences were observed in the two groups in terms of growth, haematological, immunological or clinical events.

LONGER VERSUS SHORTER REGIMENS USING THE SAME ANTIRETROVIRALS (See comparison 02)

BREASTFEEDING

One trial assessed this comparison (Thistle 2004)

Thistle 2004
An 'ultrashort' ZDV regimen (administered to mothers in labour only and to their babies for the first 3 days of life) was compared to regimen similar to 'Thai-CDC' (ZDV to mothers from 36 weeks and through labour with no treatment given to babies). There was no significant difference in HIV infection rates at birth (Efficacy -15.00%, 95% CI -152.20 to 122.20), 4-8 weeks (Efficacy 17.00%, 95% CI -41.80 to 75.80), 3 to 4 months (Efficacy 14.00%, 95% CI -38.92 to 66.92), 6 months (Efficacy 8.00%, 95% CI -42.96 to 58.96) and 12 months (Efficacy 9.00%, 95% CI -34.12 to 52.12). Furthermore, the risk of infant deaths was not statistically different during the following time periods after delivery: 4 to 8 weeks (RR 1.00; 95% CI 0.21 to 4.85), 3 to 4 months (RR 1.75; 95% CI 0.53 to 5.81), 6 months (RR 2.00; 95% CI 0.71 to 5.66) and 12 months (RR 2.00; 95% CI 0.71 to 5.66). Rates of prematurity were not significantly different (RR 1.75, 95% CI 0.53 to 5.81) and no stillbirths occurred in either group.

Adverse events
Mothers: The frequency of deaths was not significantly different (during childbirth 1 in each group, at two months postpartum 1 with 'ultrashort regimen and 0 with 'Thai-CDC' regimen, at six months postpartum 0 with 'utltrashort' regimen and 3 with 'Thai-CDC' regimen and at one year postpartum 1 with 'ultrashort' regimen and 0 with 'Thai-CDC' regimen. The trialists report that there were no significant adverse effects due to medication.
Infants: not reported.

NON BREASTFEEDING

Three trials assessed this comparison (PHPT-2; PHPT-1; Bhoopat 2005)

PHPT-2
In a programme where mothers were routinely receiving ZDV in the third trimester of pregnancy and babies were receiving one week of ZDV therapy, a single dose of NVP given to mothers in labour and to their babies soon after birth ('NVP-NVP' arm) was compared with a single dose of NVP given to mothers only ('NVP-placebo' arm). HIV infection rates at birth (Efficacy 38.00%; 95% CI -40.40 to 116.40) and at 6 months (Efficacy 29.00%; 95% CI -25.88 to 83.88) were not significantly different in the two groups. The difference in the risk of HIV infection or death at 6 months was not statistically significant (Efficacy 45.00%; 95% CI -4.00 to 94.00). Infant death rates in the first 6 months was significantly reduced in the NVP-NVP arm (RR 0.20; 95% CI 0.04 to 0.91) but differences in stillbirth rates (RR 0.25; 95% CI 0.05 to 1.17) and low birth weight (RR 0.85; 95% CI 0.60 to 1.19) were not statistically significant.

Adverse events
Mothers: Rates of serious adverse effects were reported as being similar in the comparison groups; 59% of adverse events were attributed to pregnancy, 26% to infections including HIV, 7% possibly to zidovudine (anaemia), and 7% possibly to nevirapine and other conditions.
Infants: Rates of serious adverse events were reported as being similar in the comparison groups and were attributed as follows: 11% to neonatal and obstetric conditions, 6% to congenital abnormalities, 72% to infections including HIV, 2% possibly to zidovudine (anaemia), and 9% to other causes, of which 1% involved neonatal icterus possibly due to nevirapine use.

PHPT-1
The study evaluated four regimens: 1) 'long-long' - ZDV given to mothers from 28 weeks gestation through labour and to infants from birth to 6 weeks; 2) 'long-short' - ZDV given to mothers from 28 weeks gestation through labour and to infants for the first 3 days after birth; 'short-long' - ZDV given to mothers from 35 weeks gestation through labour and to infants from birth to 6 weeks; and 4) 'short-short' - ZDV given to mothers from 35 weeks gestation through labour and to infants for the first 3 days after birth.

PHPT-1 a: 'long-long' regimen vs. 'short-long' regimen
There was no significant difference in HIV infection rates in infants at 6 months (Efficacy 24.00%; 95% CI -21.08 to 69.08) and in the risk of HIV infection or death at 6 months (Efficacy 15.00%; 95% CI -30.08 to 60.08). There was also no significant difference in infant deaths during the first 6 months (RR 0.82;

95% CI 0.24 to 2.82), stillbirth rate (RR 0.55; 95% CI 0.23 to 1.33) and the risk of premature delivery (RR 2.01; 95% CI 0.94 to 4.31). There was, however, a higher risk of low birth weight with the long-long regimen (RR 1.65; 95% CI 1.04 to 2.60)

PHPT-1 b: 'long-short' regimen vs. 'short-long' regimen
The long-short regimen significantly reduced HIV infection rate at 6 months (Efficacy 45.00%; 95% CI 1.88 to 88.12). While the risk of HIV infection or death at 6 months was also reduced this was not statistically significant (Efficacy 37.00%; 95% CI -6.12 to 80.12). There was no significant difference in the risk of infant mortality during the first 6 months (RR 1.38; 95% CI 0.44 to 4.31), premature birth (RR 1.86; 95% CI 0.84 to 4.12), low birth weight (RR 1.50; 95% CI 0.92 to 2.43) and stillbirth (RR 0.33; 95% CI 0.11 to 1.01).

As the short-short regimen seemed not to reduce transmission of HIV, it was discontinued at the first interim analysis.

Adverse events
Mothers: The rate of serious adverse events in the groups was not significantly different (deaths: 3 with 'long maternal regimen' and 8 with 'short maternal regimen'; severe anaemia: 7 with 'long maternal regimen' and 4 with 'short maternal regimen'; neutropenia: 0 with 'long maternal regimen' and 1 with 'short maternal regimen'. All maternal deaths occurred post-partum with five women dying from pneumonia, two from sepsis, one from cryptococcal meningitis, one from an AIDS-defining even and two from suicide. All cases of anaemia and neutropenia resolved spontaneously after treatment ended.
Infants: The rate of serious adverse events in the groups was not significantly different (severe anaemia: 4 with long-long, 0 with long-short, 1 with short-long, 4 with short-short courses; neutropenia or leukopenia: 7 with long-long, 3 with long-short, 5 with short-long, 2 with short-short courses; congenital abnormalities: 7 with long-long, 7 with long-short, 6 with short-long, 1 with short-short courses.

Bhoopat 2005
This study compared a long course ZDV regimen (given to women 62 to 92 days before labour and continued through labour; median 76 days) with a short course ZDV regimen (given to women from 14 to 35 days before labour and continued through labour, median 28 days). Babies did not receive antiretrovirals in either arm. HIV infection rates were not significantly different at birth (no infected babies with the 'long course' regimen vs. 1 infected baby with the 'short course regimen; Efficacy 100.00%; 95% CI -293.95 to 493.95) and 3 to 4 months (no infected babies with the 'long course' regimen vs 4 infected babies with the 'short course' regimen'; Efficacy 100.00%; 95% CI -13.68 to 213.68).

Adverse events
Not reported

REGIMENS USING DIFFERENT DRUGS AND DURATIONS OF TREATMENT (See comparison 03)

BREASTFEEDING

Three trials assessed this comparison (HIVNET 012; Taha 2003; Taha 2004)

HIVNET 012
A single dose of NVP given to mothers at the onset of labour plus a single dose of NVP given to their babies immediately after birth compared with ZDV given to mothers during labour and to their babies for a week after birth was associated with lower HIV infection rates at 4-8 weeks (Efficacy 41.00%; 95% CI 11.60 to 70.40), 3-4 months (Efficacy 39.00%; 95% CI 11.56 to 66.44), 12 months (Efficacy 36.00%; 95% CI 8.56 to 63.44) and 18 months (Efficacy 39.00%; 95% CI 13.52 to 64.48). In addition, the NVP regimen significantly reduced the risk of HIV infection or death at 4-8 weeks (Efficacy 42.00%; 95% CI 14.56 to 69.44), 3 to 4 months (Efficacy 40.00%; 95% CI 14.52 to 65.48), 12 months (Efficacy 32.00%; 95% CI 8.48 to 55.52) and 18 months (Efficacy 33.00%; 95% CI 9.48 to 56.52). There was no significant difference between the two groups for infant mortality in the first week of life (RR 2.50; 95% CI 0.49 to 12.79), in the first 4 to 8 weeks (RR 2.50; 95% CI 0.79 to 7.89) and in the first 18 months (RR 1.24; 95% CI 0.81 to 1.89). There was also no significant difference in the risk of stillbirth (RR 2.00; 95% CI 0.18 to 21.94) or low birth weight (RR 0.67; 95% CI 0.35 to 1.29).

Adverse events
Serious adverse events were defined as fatal or life threatening, permanently disabling, requiring inpatient admission, a congenital anomaly, cancer or overdose, or otherwise judged to be serious by onsite clinician, or death.
Mothers: Differences in the rate of serious maternal adverse events in the first 8 weeks were not statistically significant (15 with NVP vs 11 with ZDV; p=0.443). Deaths at 8 weeks were 0 in the NVP group and 3 in the ZDV group; p=0.081).
Infants: Rates of serious adverse events were not significantly different: at 8 weeks 29 with NVP vs 35 with ZDV; p=0.348 and at 18 months 109 with NVP vs 97 with ZDV; p=0.476). There were no significant differences in the rates of grade 3 and 4 laboratory toxic effects or grade 3 and 4 abnormalities in the alanine aminotransferase.

Taha 2003
A regimen that combined a single dose of NVP given to babies immediately after birth with ZDV given to babies for the first week of life compared to a regimen consisting of a single dose of NVP to babies only significantly reduced HIV infection at 4 to 8 weeks (Efficacy 37.00%; 95% CI 3.68 to 70.32). The study did not find a statistically significant difference in the risk of infant death in the first 4 to 8 weeks (RR 1.26; 95% CI 0.60 to 2.67).

Adverse events
The trialists reported safety analyses using data from all babies, including those excluded from primary analyses because maternal HIV infection was not confirmed. The rate of grade 3 to 4 adverse

events did not differ between groups with 31(5·6%) events in the NVP-only group and 44 (7·8%) events in the NVP + ZDV group (p=0·16). Fewer than 1% of these events in the whole study population were judged to be related to the interventions. Severe adverse events were reported as mainly related to infections or fever.

Taha 2004
This study compared the HIVNET regimen with the addition of ZDV given to babies for one week with the HIVNET regimen alone and found no significant difference in HIV infection at 4 to 8 weeks (Efficacy 13.00%; 95% CI -16.40 to 42.40) or in the risk of infant death in the first 4 to 8 weeks (RR 1.74; 95% CI 0.51 to 5.91).

Adverse events
Mothers: not reported
Infants: Grade 3 and 4 adverse events were similar between treatment groups 22 (4.9%) with NVP versus 24 (5.4%) with NVP plus ZDV. Severe adverse events were considered to be mainly due to infections; of the 46 grade 3 or 4 adverse events, 25 cases (54%) were coded as pneumonia, diarrhoea, or malnutrition possibly related to infections. Severe haematological changes were observed in 15 (4.39%) of 342 of the NVP plus ZDV group and 7 (2.13%) of 329 of the NVP only group (p= 0.13).

NON BREASTFEEDING

Five trials assessed this comparison (PACTG 316; SAINT; Gray 2006; Kiarie 2003; Gray 2005)

PACTG 316
In a population in which mothers were receiving 'standard' ARV for HIV infection a single dose of NVP given mothers in labour plus a single dose of NVP given to babies immediately after birth (HIVNET 012 regimen) compared with placebo did not result in a statistically significant difference in HIV infection rates at birth (Efficacy 2.00%, 95% CI -143.04 to 147.04) and 4 to 8 weeks (Efficacy 13.00%, 95% CI -83.04 to 109.04) or in deaths at 4 to 8 weeks (RR 0.60, 95% CI 0.14 to 2.50). There was also no significant difference in stillbirth rates (RR 2.99; 95% CI 0.12 to 73.33), low birth weight (RR 1.14; 95% CI 0.85 to 1.53) or rates of prematurity (RR 1.05, 95% CI 0.83 to 1.32).

Adverse events
Mothers: The rates of severe adverse events did not differ significantly (deaths after delivery: 2 with NVP and 1 with placebo; grade 3 and 4 toxicity - rash 1 with NVP and 1 with placebo; non-rash toxicity 40 with NVP and 38 with placebo; and hepatic toxicity 5 with NVP and 5 with placebo)
Infants: The rates of severe adverse events did not differ significantly (grade 3 and 4 toxicity - rash 1 with NVP and 3 with placebo; non-rash toxicity 235 with NVP and 195 with placebo; and hepatic toxicity 1 with NVP and 2 with placebo

SAINT
A regimen of ZDV plus 3TC given to mothers in labour and for a week after delivery and to their infants for a week after birth (similar to PETRA arm b) was compared with a regimen of NVP given to mothers in labour and immediately after delivery plus a single dose of NVP to their babies immediately after birth (similar to HIVNET 012). There was no significant difference in HIV infection rates at 4 to 8 weeks (Efficacy 24.00%; 95% CI -5.40 to 53.40), the risk of low birth weight (RR 1.41; 95% CI 0.45 to 4.42) and infant death rates at 4 to 8 weeks 1.01 (0.54 to 1.89)

Adverse events
Mothers: The rate of serious adverse events was reported as similar in the two groups: There were 5 deaths (0.8%) with NVP vs 4 (0.6%) deaths with ZDV plus 3TC. No hepatic or haematological adverse events were reported for either group.
Infants: The rates of serious adverse events (clinical or laboratory abnormalities) were not significantly different: 9.0% in the NVP group and 10.4% in the ZDV plus 3TC group. The most frequent serious adverse events were respiratory system disorders (including asphyxia, respiratory distress syndrome, aspiration, and dyspnoea) (NVP: 4.1%; ZDV plus 3TC: 4.2%) and infections (NVP: 2.6%; ZDV plus 3TC: 3.2%).

Gray 2006
This study compared various ARV drugs given to mothers from 34 to 36 weeks and through labour as well as the same drugs given to their babies for 6 weeks

Gray 2006 a: d4T versus ZDV
There was no significant difference in the rates of HIV infection at birth (Efficacy 27.00%; 95% CI -121.96 to 175.96), 4 to 8 weeks (Efficacy -120.00%; 95% CI -300.32 to 60.32), 3 to 4 months (Efficacy -145.00%; 95% CI -331.20 to 41.20) and 6 months (Efficacy -116.00%; 95% CI -280.64 to 48.64). There was also no significant difference in the risk of infant mortality in the first 6 months (RR 2.97; 95% CI 0.83 to 10.61).

Gray 2006 b: ddI versus ZDV
HIV infection between the two groups did not differ significantly at birth (Efficacy 53.00%; 95% CI -88.12 to 194.12), 4 to 8 weeks (Efficacy -42.00%; 95% CI -206.64 to 122.64), 3 to 4 months (Efficacy -113.00%; 95% CI -291.36 to 65.36) and 6 months (Efficacy -89.00%; 95% CI -247.76 to 69.76). There was no significant difference in the risk of infant mortality in the first 6 months (RR 1.94; 95% CI 0.50 to 7.52).

Gray 2006 c: d4T plus ddI versus ZDV
No significant difference in the rates of HIV infection were found at birth (Efficacy 49.00%; 95% CI -96.04 to 194.04), 4 to 8 weeks (Efficacy -24.00%; 95% CI -126.92 to 174.92), 3 to 4 months (Efficacy -1.00%; 95% CI -157.80 to 155.80) and 6 months (Efficacy 18.00%; 95% CI -119.20 to 155.20). There was also no significant difference in the risk of infant mortality in the first 6 months (RR 0.66; 95% CI 0.11 to 3.86).

Adverse events

Mothers: Rates of serious adverse events were low and did not differ significantly between the groups. There were two deaths (1 woman on ZDV died of haemorrhage after an extrauterine pregnancy and 1 woman on d4T plus ddI due to left ventricular dysfunction; neither death was judged to be due to treatment).
Infants: Grade 3 and 4 adverse events were more frequent with d4T plus ddI (18%) and ZDV (14%) than with either d4T (9%) or ddI (6%). Death, gastroenteritis and pneumonia were the most common serious adverse events reported and most were considered not to be related to treatment.

Kiarie 2003
A 'Thai CDC' regimen compared with 'HIVNET 012' regimen found no significant difference in HIV infection at 4 to 8 weeks (Efficacy 58.00%; 95% CI -4.72 to 120.72). There was also no difference in the risk of infant mortality in the first 4 to 8 weeks (RR 0.99; 95% CI 0.21 to 4.72), stillbirth (RR 1.48; 95% CI 0.25 to 8.58), prematurity (RR 1.97; 95% CI 0.37 to 10.42) and low birth weight (RR 1.97; 95% CI 0.18 to 21.24).

Adverse events
Not reported.

Gray 2005
A single dose of NVP given to babies immediately after birth compared to ZDV given to babies for the first 6 weeks of life did not result in a statistically significant difference in HIV infection rates at 4-8 weeks (Efficacy 35.00%; 95% CI -10.08 to 80.08) and 3 to 4 months (Efficacy 40.00%; 95% CI -1.16 to 81.16). Infant mortality in the first 4 to 8 weeks was also similar in the two groups (RR 1.15; 95% CI 0.52 to 2.54)

Adverse events
There was no significant difference in the overall rate of serious adverse events in infants between ZDV and NVP (118 with ZDV versus 94 with NVP; none were thought to be due to study medication and most were due to infections such as pneumonia (22 with ZDV versus 18 with NVP) and gastroenteritis (20 with ZDV versus 15 with NVP). Other serious events included birth-related conditions (14 with ZDV versus 6 with NVP), physiological jaundice (10 with ZDV versus 5 with NVP) and neonatal septicaemia (7 with ZDV versus 13 with NVP). Of these serious adverse events, 17 (18.1%) in the NVP arm and 36 (30.5%) in the ZDV arm were related to HIV.

DISCUSSION

Our review confirms that antiretroviral treatment administered in the perinatal period compared with placebo lowers the risk of mother-to-child transmission of HIV. ZDV has been the most extensively studied and forms a component of treatment in all eighteen trials included in this review. In a non-breastfeeding population a long course of ZDV used in the antepartum and intrapartum periods and postnatally in babies led to an impressive 66% reduction in HIV infection risk in babies at 18 months (PACTG 076). Important benefits were also found with shorter courses of ZDV monotherapy, although these appear to be less pronounced, with effects on HIV infection rates at 4 to 8 weeks ranging from halving to a one third reduction compared with placebo. Among the shorter course regimens, a combination of ZDV and 3TC commenced at 36 weeks and continued through labour and up to a week postpartum and given to babies for the first week of life appears to be highly worthwhile. Compared with placebo the efficacy of this regimen in reducing HIV infection risk at 4 to 8 weeks was as much as 63% (PETRA).

We found no trials that have evaluated the effects on mother-to-child transmission of NVP monotherapy against placebo. In a breastfeeding population a single dose of nevirapine given to mothers at the onset of labour and to their babies soon after birth compared with a suboptimal course of zidovudine given to mothers only during labour and to their babies for the first week of life reduced the risk of mother-to-child transmission at 4 to 8 weeks by about 40% with the benefit persisting at 18 months of life (HIVNET 012). A regimen comparable to HIVNET 012 but with mothers receiving an additional dose of NVP postpartum resulted in similar HIV infection rates at 4 to 8 weeks as a regimen consisting of ZDV plus 3TC given to mothers during labour and for one week postpartum and to babies for one week after birth (PETRA regimen B) (SAINT). One small trial comparing the HIVNET 012 and Thai CDC regimens failed to demonstrate a significant difference on HIV transmission. (Kiarie 2003). Furthermore, in a population where mothers were routinely receiving ZDV in the last trimester of pregnancy and their babies were receiving ZDV in the first week of life, the HIVNET regimen compared with a single dose of NVP given only to mothers did not result in a significant reduction in HIV transmission at 6 months (PHPT-2). The trial did, however, find a reduction in HIV infection and death at 6 months which was marginally significant as well as a significantly lower risk of infant deaths in the first 6 months with the HIVNET 012 regimen (PHPT-2) The addition of ZDV treatment to babies in the first week after delivery in addition to the HIVNET 012 regimen had no significant effect on HIV transmission compared with an HIVNET regimen alone (Taha 2004).

Length and timing of antiretroviral treatment

With ZDV-based regimens, the length of treatment seems to influence transmission rates with a longer antenatal component being the most important. In placebo-controlled trials ZDV given to mothers from 36 weeks gestation and during labour (Thai-CDC; RETRO-CI) was more effective than ZDV given from 36 to 38 weeks, through labour and continued for 7 days postpartum (DITRAME), regardless of whether babies breast fed. Similarly, in the PETRA study a combination of ZDV and 3TC given to mothers from 36 weeks gestation, during labour and continued for a week postpartum as well as to their babies for a week (regimen A) resulted in a greater reduction in HIV infection rate at 4

to 8 weeks compared with placebo than the same treatment but without an antenatal component (regimen B), a third arm using the combination treatment during labour only (regimen C) was found to be no better than placebo. Furthermore, a direct head-to-head comparison of ZDV given to mothers from 28 weeks gestation and during labour and to babies for 3 days after delivery ('long-short' regimen) resulted in a lower rate of HIV infection or HIV infection or death at 6 months than ZDV given to mothers from 35 weeks and during labour and to infants for 6 weeks after delivery ('short-long' regimen) (PHPT-1). On the other hand, two smaller trials comparing longer and shorter zidovudine regimens found no difference between their effects on HIV infection rates in babies (Thistle 2004; Bhoopat 2005).

Antiretroviral treatment in the antenatal and intrapartum periods is not an option for HIV infected women who present late for delivery. In these cases, post-exposure prophylaxis limited to babies can be valuable. In one trial, a single dose of NVP immediately after birth plus ZDV for the first 6 weeks of life compared with a single dose of NVP only reduced infection rates by 37% at 4 to 8 weeks (Taha 2003). A further trial compared a single dose of NVP immediately after birth with ZDV given for the first 6 weeks and did not demonstrate a statistically significant difference in the rate of infection (Gray 2005).

Influence of breastfeeding

Breast milk is a source of HIV and has been shown to increase the of mother-to-child transmission of the virus. It is not clear to what extent breastfeeding influences the efficacy of antiretroviral treatment as only a few trials in breastfeeding populations (all of them in Africa) report HIV transmission rates beyond 4 to 8 weeks and the results of these studies are conflicting (DITRAME, PETRA; Thistle 2004; HIVNET 012) In the DITRAME trial the initial reduction in perinatal transmission was maintained at 18 months; this was also the case in the HIVNET 012 trial. On the other hand, in the PETRA study early reductions in HIV infection rates as well as HIV infection or death at 4 to 8 weeks declined and became statistically non-significant by 18 months. One trial did not find a difference in HIV infection rates at any stage of follow up (Thistle 2004)

It should be noted that reliable information on the extent or type of breastfeeding (mixed versus exclusive) across studies was not available to us; neither were we able to take into account other factors influencing transmission risk, such as maternal viral load. A recent individual patient data meta-analysis compared the efficacy of various antiretroviral regimens in reducing mother-to-child transmission risk at 6 weeks in African breastfeeding populations using multivariate methods to adjust for maternal CD4 count, breastfeeding and birthweight in (Leroy 2005). The authors concluded that the longest course of ZDV and 3TC (PETRA Regimen A) was more effective than shorter courses of the same drug combination and more effective than any other antiretroviral monotherapy regimen. These results concord with the findings of our review.

Adverse effects

None of the trials in our review found statistically significant differences in the rates of serious or life threatening events in either mothers or babies. Mild transient anaemia seems to occur and is most frequently seen in mothers and babies exposed to the long course PACTG076 regimen. No cases of lactic acidosis or hepatic steatosis were found in the trial evaluating d4T and ddI and nevirapine did not significantly increase the incidence of severe hepatoxicity or rash. Furthermore, antiretrovirals did not increase the likelihood of congenital defects, abnormal growth patterns or the occurrence of childhood cancers.

The emergence of resistant mutations following the use of antiretroviral regimens in the prevention of vertical transmission is, however, a cause for concern as this may potentially compromise future treatment of infected mothers and babies including future efforts to reduce mother-to-child transmission (Eshleman 2005a; Eshleman 2005b; Johnson 2005; Eshleman SH, Gu3). A single dose of NVP was associated with an increase in resistant mutations in a subsample of mother-infant pairs in the HIVNET 012 trial (Eshleman 2001). It has also been shown that a combination of zidovudine and 3TC does not prevent the emergence of 3TC resistance (Mandelbrot, 2001) These resistant mutations disappear with time and their clinical importance is therefore by no means clear, yet the finding that viral response to NVP treatment may be reduced in women previously receiving a regimen comprising a single dose NVP plus a short course of ZDV as prophylaxis is worrying (Jourdain 2004). Further research is needed to clarify this issue.

Strengths and limitations of our review

As recommended for all Cochrane review we conducted an extensive and comprehensive search of multiple electronic bibliographic databases and searched conference abstracts and conducted handsearching for relevant African medical journals to identify eligible trials for inclusion. We also fully described the methodological quality of all included trials. Where possible, we also engaged directly with trialists to obtain missing data or for clarification where this was required. The data presented in this review is thus likely to be a full account of the trial evidence. Completed but as yet unpublished trial data, such as that of the SIMBA trial (SIMBA), will be included in the following update of this review.

Heterogeneity of studies

Comparison of the results of the trials included in this review is a challenging task given the differences in study populations, trial methodology and treatment regimens. In addition, the methods for assessing HIV transmission varies across studies; both the criteria for establishing HIV infection and the sensitivities of tests have changed over time (Hill 1999). As a result of these differences, any indirect comparisons between regimens across trials must there-

fore be treated with considerable caution. To reduce the amount of clinical heterogeneity between trials, we stratified our analysis according to intervention and choice of feeding. Despite this stratification, we were unable to statistically combine the results the trials using meta-analytic techniques. Given that most of the individual trials were small to moderate in size and that meta-analysis was not possible we cannot rule out the play of chance as an explanation of the findings reported, neither can we rule out the possibility that important but infrequent adverse effects were missed.

Determination of infection status

Determining exactly when transmission occurs is complex given that the age of infection is known only to be between the ages at the last negative and first positive tests (Ghent 2001). The risk of paediatric infection over time also depends on whether or not a mother continues to breastfeed, but few trials collect and provide accurate information on the exact age of complete weaning (Ghent 2001). In some trials, it has been noted that infants may become infected well after the reported time of weaning (Ghent 2001). The Ghent Working Group, comprising methodologists and trialists, has developed a consensus approach to the statistical analysis applicable across all MTCT trials to facilitate reviewing and meta-analysing such trial data. They stress the importance good quality information about age at weaning to estimate transmission probabilities in breastfeeding populations in future trials. They also provide a framework for statistical analysis using interval-censored data similar to what we employed in this review. It is important to note that interval-censored data analysis as recommended by the Ghent group does not estimate the 'time to infection' but 'time to detection' of HIV, which is always dependent on the testing schedule. Ideally, future trials should consider using standardised testing schedules so that better comparisons can be made between trials.

Multiple births

Because inclusion of all children from multiple births in an analysis violates the requirement of most statistical methods that observations be independent of one another (Ghent 2001), trials have to account for this and we described the different methods each trial used to do this in our review (see Table of Included Studies). However, the Ghent group recommend that all future trials use the first born baby of each multiple birth in studies of MTCT transmission. As observational studies have shown that the first born of twins has a higher risk of infection (Ghent 2001), using this method of analysis would provide a more conservative estimate of efficacy but would ensure consistency between study comparison groups and between trials.

Short-term and long-term efficacy

HIV infection in specimens collected between the first day of the neonatal period and day 60 can be used to effectively assess short-term efficacy (Alioum 2003). Long-term efficacy estimates of HIV infection are more problematic. Estimates may be biased if only one test is conducted between 15 and 24 months of age because loss to follow-up and deaths are unlikely to be evenly distributed between trial arms (Alioum 2003). It has therefore been suggested that HIV-free survival provides a less biased estimate of long-term efficacy (Ghent 2001). The difficulties of providing such long-term follow-up beyond trial termination may not always be feasible where public health resources are limited and such ideal information may rarely be available.

AUTHORS' CONCLUSIONS

Implications for practice

In countries where HAART is not yet routinely available, shorter, less expensive antiretroviral regimens for reducing mother-to-child transmission should be considered, as there is good evidence that the benefits associated with such an intervention outweigh the potential risks. It is not entirely clear which regimen is best but a combination of ZDV and 3TC given to mothers in the antenatal, intrapartum and postpartum periods and to babies for a week after delivery or a regimen involving a single dose of NVP given to mothers in labour and babies immediately after birth seems to be effective and feasible. Zidovudine monotherapy is also useful, especially if it includes a long antenatal treatment component. Where HIV infected women present late for delivery post-exposure prophylaxis for the infant with a single dose of NVP immediately after birth plus ZDV for the first 6 weeks of life is beneficial.

Implications for research

The relative protective effect of perinatal antiretroviral regimens in babies that are breast fed and formula fed requires further study. Research on the long term impact of drug resistance on future treatment of infected mothers and babies is urgently needed; regimens that reduce the likelihood of resistant mutations emerging should be developed and evaluated. Future trials should as far as possible use standardised methods that will allow reliable comparisons of treatment effects in different trials and include adequate follow up to fully assess long term safety of antiretrovirals.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Bhoopat 2005**
Methods	Generation of allocation sequence: Unclear - Participant were 'randomised'.
	Allocation concealment: Unclear - Method not stated
	Blinding: Participants - Unclear; Providers- Unclear; Assessors - Unclear
	Exclusions: Overall - 0% (0/50); Short course ZDV - 0% (0/27); Long course ZDV - 0% (0/23)
Participants	50 women recruited from 2 hospitals in Thailand. Period not stated.
	Inclusion criteria: HIV-1 positive women who had received ZDV for at least 2 weeks, agreed not to breastfeed, and had laboratory values within accepable limits: HB>8g/dL, absolute neutrophil count >750 cell/cubic mm, SGPT <5x ULN, creatinine <1.5mg/dL
	Exclusion criteria: Did not fulfill the above criteria, maternal or fetal condition or treatment contradicating ZDV use, oligohydramnios, unexplained polyhydramnios or in utero anaemia or medical need for HAART.

Characteristics of included studies (*Continued*)

Interventions	Short-term ZDV arm - MOTHER - ZDV 300mg BD lasting from 14 to 35 days before labour (median 28 days), then 300mg at onset of labour and every 3 hours from labour to delivery. Long-term ZDV arm - MOTHER - ZDV 300mg BD lasting from 62 to 92 days before labour (median 76 days), then 300mg at onset of labour and every 3 hours from labour to delivery.
Outcomes	HIV-1 infection (subtype E)in infants at 6 weeks, 4 months and 6 months. Measured by DNA PCR. Detection of HIV-1 (subtype E) in the placenta
Notes	All women gave written consent. Ethical approval not reported.
Allocation concealment	B – Unclear

Study	**DITRAME**
Methods	Generation of allocation sequence: Adequate - central, computerised randomisation in blocks of 10 and stratified by centre. Allocation concealment: Adequate - sequentially numbered, sealed packs prepared by an independent, central pharmacy. Blinding: Participants - Yes; Providers- Yes; Assessors - Unclear Exclusions: Overall - 7.4% (32/431); ZDV - 6.5% (14/214); Placebo - 8.3% (18/217)
Participants	431 women recruited from public clinics in Cote d'Ivoire and Burkina Faso from September 1995 to February 1998. Inclusion criteria: Women aged 18+ years positive for HIV-1 or both HIV-1 and HIV-2 who presented before 32 weeks gestation who lived in and planned to give birth in the area. Exclusion criteria: Sickle cell markers SS, CC or SC haemoglobin, haemoglobin <7 g/dL, absolute neutrophils <0.75 X 109, alanine and aspartate aminotranferases >2.5X standard value fo the laboratory.
Interventions	ZDV arm: MOTHER 300mg twice daily from 36-38 weeks until onset of labour; 600 mg at start of labour and 300mg twice daily until 7 days after birth. As the formulation of ZDV changed from 250mg to 300mg the daily dose was 500mg rather than 600mg in the early part of the trial. INFANTS: no treatment
Outcomes	Primary: HIV-1 infection in infant measured by sequential DNA PCR at 1-8, 45, 90 and 180 days and analysed by the Kaplar-Meier method. Other: Mortality in infants
Notes	>95% infants were breastfed The study was approved by IRBs in Burkina Faso, Cote d'Ivoire and France. Women gave written informed consent.
Allocation concealment	A – Adequate

Study	**Gray 2005**
Methods	Generation of allocation sequence: Adequate - computerised randomisation Allocation concealment: Adequate - allocation provided to study nurses in sequentially numbered, non-transparent envelopes. Blinding: Participants - No; Providers- No; Assessors - Unsure Exclusions: Overall - 31.7% (333/1051); ZDV - 31.1% (166/533); NVP - 32.2% (167/518)
Participants	1530 women recruited from 3 public hospitals in South Africa from October 2000 to September 2002.

	Inclusion criteria: Infants included if mother HIV-1 Exclusion criteria: Infant preterm, weighed <1200g, required ventilation, unable to take oral medication, had congenital abnormalities.
Interventions	NVP arm: INFANT - NVP suspension 10mg/ml as a single oral dose at 2mg/kg within 24 hours of delivery ZDV arm: INFANT - zidovudine syrup 10mg/ml as an oral dose at 4mg/kg within 24 hours of delivery, then 12 hourly for 6 weeks after birth.
Outcomes	PRIMARY Postuterine (intrapartum or early postpartum) HIV infection at 12 weeks. Postuterine infection = HIV negative at birth and positive on day 10 or more. HIV infection confirmed by HIV-1 DNA PCR. Serious adverse events SECONDARY Influence of breastfeeding on effectiveness
Notes	14% infants in ZDV and 18% in NVP breastfed The study was approved by local IRBs. Women gave informed consent.
Allocation concealment	A – Adequate

Study	**Gray 2006**
Methods	Generation of allocation sequence: Unclear - 'randomised' study Allocation concealment: Unclear - method not stated. Blinding: Participants - No; Providers- No; Assessors - Unsure Exclusions: Overall - 2.9% (11/373); d4T - 2.2% (2/93); ddI - 1.1% (1/95); d4T plus ddI 5.4% (5/93) ; ZDV 3.4% (3/89)
Participants	373 women recruited from a public hospital in Soweto, South Africa from May 1999 to May 2000. Inclusion criteria: HIV-1 infected ARV naiive women aged 18+ years at 34-36 weeks gestation, prepared to formula feed, willing to have their infants followed up for 6 months after birth, laboratory values within acceptable limits: serum creatinine <=1.5x ULN, total serum lipas <=1.4x ULN, aspartate aminotranferase and alanine aminotransferase <=5x ULN. Exclusion criteria: severe fetal abnormality; >= 3 fetuses; newly diagnosed HIV opportunistic infections, malignancy, or other condition requiring acute therapy at time of enrollment; active drug abuse; history of pancreatitis; past or present symptoms for grade 2 or greater bilateral peripheral neuropathy.
Interventions	d4T arm - MOTHER - d4T 40mg (or 30mg if wt <60kg) BD during pregnancy through labour and delivery plus an additional dose about 1 hr before delivery. INFANT - d4T in liquid form 1mg/kg BD within 36 hrs of birth to 6 weeks after birth. ddI arm - MOTHER 200mg (or 125 mg if wt <60 kg) BD during pregnancy through labour and delivery. plus an additional dose about 1 hr before delivery. INFANTS - ddI in liquid form 120mg/sqm BD within 36 hrs of birth to 6 weeks after birth. d4T plus ddI arm - As for d4T and ddI dosing schedule above ZDV arm - MOTHER ZDV 300mg BD during pregnancy through labour and delivery. plus an additional dose about 1 hr before delivery. INFANTS - ZDV 4mg/kg BD within 36 hrs of birth to 6 weeks after birth.
Outcomes	HIV-1 infection in infant at birth, 6, 12 and 24 weeks. Measured by DNA PCR. Adverse events in infant and mother.
Notes	Mothers gave written informed consent. Study approved by Gauteng Department of Health Provincial Review Committee and University of Witwatersrand Committte for Research on Huamn Subjects and the South African Medicines Control Council.

Allocation concealment	B – Unclear

Study	**Gray 2006 a**
Methods	
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	A – Adequate

Study	**Gray 2006 b**
Methods	
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	A – Adequate

Study	**Gray 2006 c**
Methods	
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	A – Adequate

Study	**HIVNET 012**
Methods	Generation of allocation sequence: Adequate - computerised randomisation in permuted blocks of 12. Allocation concealment: Adequate - sequentially numbered treatment packs prepared by a study pharmacist, according to allocation schedule. Blinding: Participants - No; Providers- No; Assessors - Yes Exclusions: Overall - 2.6% (17/645); ZDV - 3.5% (11/313); NVP - 1.6% (5/313); Placebo - 5.2% (1/19)
Participants	645 women recruited from antenatal clinics at a single hospital in Kampala, Uganda from November 1997 to April 1999. Inclusion criteria: HIV-1 positive women aged 18+ years who were > 32 weeks gestation and lived near the study hospital Exclusion criteria: Current antiretroviral or HIV immunotherapy, uncontrolled hypertension, haemoglobin <75g/L, blood creatinine >1.5 mg/dL, alanine transaminase concentration >3x ULN, chronic alcohol or drug use, benzodiazepine use, anticoagulant therapy, magnesium sulphate within 2 weeks of enrolment or likely to be needed during labour or delivery.
Interventions	NVP arm: MOTHER - Single 200mg oral dose at onset of labour; INFANT - single oral dose 2mg/kg 72 hours after birth or at hospital discharge (whichever was soonest) ZDV arm: MOTHER - 600mg orally at onset of labour and 300mg 3 hourly during labour; INFANT - zidovudine syrup, 4mg/kg twice daily for 7 days after birth.

Characteristics of included studies (*Continued*)

	PLAC arm: Discontinued after the results of the Thailand trial found that a short course of ZDV given in antepartum and intrapartum period was effective.
Outcomes	Primary - HIV infection and HIV-1 free survival (i.e. time to death or first positive HIV-1 RNA assay) at 6-8 weeks, 14-16 weeks and 18 months. HIV infection confirmed by HIV-1 RNA PCR or culture Other: Adverse events in mother at 6 weeks postpartum Adverse events in baby up to 18 months
Notes	99% infants breastfed The study was approved by IRBs in Uganda and the USA. Women gave written informed consent.
Allocation concealment	A – Adequate

Study	**Kiarie 2003**
Methods	Generation of allocation sequence: Unclear - 'block randomisation' Allocation concealment: Unclear - 'sealed envelopes' Blinding: Participants - No; Providers- No; Assessors - Unsure Exclusions: Overall - 20.9% (29/139); 'Thai CDC' - 21.4% (15/70); HIVNET 012 - 20.3% (14/69)
Participants	188 women recruited from an antenatal clinic at a tertiary hospital in Nairobi, Kenya from November 1999 (end date of enrollment not stated). Trial ended in January 2001. Inclusion criteria: HIV-1 positive women at <35 weeks, intended to remain in the city until 6 weeks post-delivery and had no contraindications to ARVs.
Interventions	'THAI CDC' arm: Treatment not specified 'HIVNET 012' - Treatment not specified
Outcomes	HIV-1 infection at 6 weeks. Measured by DNA PCR Compliance to treatment
Notes	All women gave written informed consent. Ethics approval not mentioned.
Allocation concealment	B – Unclear

Study	**Limpongsanurak 2001**
Methods	Generation of allocation sequence: Unclear - randomised in permuted blocks of 4. Allocation concealment: Unclear. Blinding: Participants - Yes; Providers- Yes; Assessors - Yes Exclusions: Overall 4.4% (8/182); ZDV (3.3%) 3/90; Plac 5.4% (5/92)
Participants	182 women enrolled at 3 public sector hospitals in Bangkok, Thailand between September 1995 and December 1996. Inclusion criteria: HIV-1 positive women aged 15 to 40 years at 37 weeks gestation with no history of ARV use, no intention to breastfeed, no fetal abnormality, haemoglobin >8g/dl and willing to bring child for follow up at 6 months after delivery.
Interventions	ZDV arm: MOTHER - ZDV 250 mg orally twice daily from 38 weeks gestation until onset of labour then ZDV intravenously at 2mg/kg for first hour of labour followed by 1mg/kg/hr until delivery. INFANTS - no treatment

	PLAC arm: Identical placebo capsules and 5% intravenous dextrose in half strength normal saline in intrapartum period at same dosing schedule.
Outcomes	HIV-1 infection in infants by DNA PCR at birth, 1, 3 and 6 months. Infants positive if two of three results at 1, 2 and 6 months were positive and not infected if all results were negative.
Notes	No breastfeeding Study approved by ethics committee at Chulalongkorn University in Thailand. All women gave written informed consent. Study terminated early because of antiretrovirals becoming freely available to all pregnant HIV women in early 1996.
Allocation concealment	B – Unclear

Study	**PACTG 076**
Methods	Generation of allocation sequence: Unclear. Randomisation stratified by gestational age (14-26 weeks vs >26 weeks). Allocation concealment: Unclear. Blinding: Participants - Yes; Providers - Unclear; Assessors - Unclear: trial described as "double-blind" Exclusions: Overall - 23.9% (114 /477); ZDV - 24.6% (59/239); Placebo - 23.1% (55/238)
Participants	477 women recruited from "59 centers" in USA and France from April 1991 to December 1993. Inclusion criteria: HIV +ve women at 14-34 weeks gestation with CD4 count >200, no indication for ARV and laboratory criteria meeting the following criteria: Haemoglobin >=8 g/dL, absolute neutrophils <=1000 cells per cubic mm, platelets >100 000 per cubic mm, serum alanine aminotranferase <= 2.5X ULN, serum creatinine <= 1.5 mg per dL or 8 hr urinary creatinine clearance >70 ml per minute. Exclusion criteria: Life threatening fetal abnormality, anomaly that may increase fetal concentration of ZDV or metabolites, oligohydramnios in second semester or unexplained oligohydramnios in third trimester, fetal hydrops, ascites , other evidence of fetal anaemia, any ARV treatment during current pregnancy, immunotherapy, anti-HIV vaccine, cytolytic chemotherapeutic agents, radiation therapy. Number of women screened not stated, 477 were randomised of which 409 gave birth to live infants.
Interventions	ZDV arm. MOTHERS: ZDV 100mg orally x 5 per day from time of presentation (14 - 34 weeks) until onset of labour; intravenous ZDV 2mg/kg loading dose over one hour follwed by 1 mg/kg/h until delivery. INFANTS: ZDV syrup 2mg/kg six hourly for six weeks, beginning 8 - 12 hrs after birth Placebo arm: Placebo to mothers and infants
Outcomes	HIV infection in at 18 months estimated by Kaplan-Meier method. Adverse events in mothers and infants.
Notes	No infants were breastfed The study was approved by IRB of each participating centre in the US and by the Committee for the Protection of Persons in Biomedical Research in France. Women (and the father of the child when available) gave written informed consent). Study stopped by DSMB at first interim analysis on 20 December 1993.
Allocation concealment	B – Unclear

Study	**PACTG 316**
Methods	Generation of allocation sequence: unclear. Randomisation stratified by type of standard ARV treatment and baseline CD4 count. Allocation concealment: Not stated

Characteristics of included studies (*Continued*)

	Blinding: Participants - Yes; Providers- Yes; Assessors - Unclear Exclusions: Overall - 17.1% (258/1506); NVP - 16.3% (123/754), Plac -18.0% (135/752)
Participants	1506 women receiving standard ARV therapy recruited from "PACTG sites" in USA, Europe, Brazil and Bahamas enrolled from May 1997 to June 2000. Inclusion criteria: HIV +ve women at 28+ weeks gestation (later changed to 20+ weeks). Exclusion criteria: Enrolled in other perinatal treatment trials, previous treatment with non-nucleoside reverse transcriptase inhibitors, hypersensitivity to benzodiazipines, ALT >10 ULN, mother intended to breastfeed, fetus with life threatening abnormality
Interventions	NVP arm: MOTHER - one 200mg dose orally at onset of labour. INFANT - single oral dose 2mg/kg 48-72 hours after birth. If labour continued mother given addition NVP dose. PLAC arm: Corresponding placebo to mother and infant Co-interventions: All mothers received 'standard' ARV therapy as determined by the clinicians which could include any licensed ARV except NNRTI.
Outcomes	Primary: HIV infection in infant - HIV DNA assay and/or culture positive if 2 tests positive on two different specimens Grade 3 and 4 toxicity in mothers and infants.
Notes	No breastfeeding The study was approved by IRBs at each study site and mothers gave written informed consent. Twin births assessed as a single transmission if either infant was infected.
Allocation concealment	B – Unclear

Study	**PETRA**
Methods	Generation of allocation sequence: Unclear - block randomised by site Allocation concealment: Adequate - 'pre-randomised packs labelled by patients' numbers' 'All the steps following the preparation of the study medication batches were masked.' Blinding: Participant - Yes; Provider - Yes; Assessor - Unclear Exclusions: Overall - 29.5% (430/1457); Arm A - 26.7% (98/366), Arm B- 32.3% (120/371), Arm C-30.7% (113/368), Placebo -28.1% (99/352)
Participants	Participants recruited from four large public hospitals and one missionary hospital in South Africa, Tanzania and Uganda and enrolled from June 1996 to January 2000. Enrollment in the placebo arm was disontinued in February 1998. Inclusion criteria: HIV-1 +ve women with gestational age <36 weeks, age > 18 years or legal age of consent, Hb>8g/L and 18 months follow up possible. Exclusion criteria: No severe fetal abnormalities or life threatening disease and Hb 23,273 women were screened, 1,797 were randomised of which 1,457 gave birth before 18 February 1998.
Interventions	Arm A. MOTHERS: Oral zidovudine (ZDV) plus Lamivudine (3TC) from 36 weeks gestation until 7 days after delivery. ZDV 300mg/3TC 150mg twice daily from 36 weeks, ZDV 300mg/3TC 150mg at onset of labour, ZDV 300mg 3 hourly and 3TC 150mg 12 hourly during labour and ZDV 300mg/3TC 150mg twice dail for 7 days postpartum. INFANTS: ZDV 4mg/kg plus 3TC 2mg/kg twice daily for first 7 days after birth

	Arm B. MOTHERS: Oral zidovudine (ZDV) plus Lamivudine (3TC) from the start of labour until 7 days after delivery. Dosing schedule the same as for Arm A except for the loading dose at the start of labour of ZDV 600mg/3TC 150mg. INFANTS: ZDV plus 3TC for first 7 days after birth as for Arm A. Arm C. MOTHERS: ZDV plus 3TC during labour only. ZDV 600mg/3TC 150mg at onset of labour followed by ZDV 300mg 3 hourly and 3TC 150mg 12 hourly until delivery. INFANTS: None Arm D. Matching Placebo. Co-interventions - MOTHERS: Multivitamins postnatally; INFANTS: Cotrimoxazole prophylaxis up to months after birth
Outcomes	HIV-1 infection at 6 weeks and at 18 months HIV-1 infection or death at 18 months Adverse events: Grade 3 and 4 events on the Adverse Event Toxicity Scale in mothers and infants Congenital abnormalities Neurological events up to 18 months after birth
Notes	74% INFANTS BREASTFED There was no mention of ethics approval. All women gave written informed consent. The trial management committee decided to discontinue enrolment into the placebo arm after 18 February 1998 because a trial conducted in Thailand had found a 50% efficacy rate for reducing mother to child transmission of HIV with short-course ZDV. Following this date 297 women were enrolled into the 3 remaining arms - the distribution of these participants across study the sites was different to that of women randomised earlier. Only the 1457 women randomised before 18 February 1998 are included in the main analysis.
Allocation concealment	A – Adequate

Study	**PETRA a**
Methods	
Participants	
Interventions	
Outcomes	
Notes	74% INFANTS BREASTFED There was no mention of ethics approval. All women gave written informed consent. The trial management committee decided to discontinue enrolment into the placebo arm after 18 February 1998 because a trial conducted in Thailand had found a 50% efficacy rate for reducing mother to child transmission of HIV with short-course ZDV. Following this date 297 women were enrolled into the 3 remaining arms - the distribution of these participants across study the sites was different to that of women randomised earlier. Only the 1457 women randomised before 18 February 1998 are included in the main analysis.
Allocation concealment	A – Adequate

Study	**PETRA b**
Methods	
Participants	
Interventions	
Outcomes	
Notes	

Allocation concealment	A – Adequate

Study	**PETRA c**
Methods	
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	A – Adequate

Study	**PHPT-1**
Methods	Generation of allocation sequence: Unclear - randomised in blocks of 6 and changed to 5 after interim analysis. Allocation concealment: Adequate - treatment packs were centrally prepared and identified by random numbers. Blinding: Participants - Yes; Providers- Yes; Assessors - Unclear Exclusions: First interim analysis (4 December 1998): Overall 3.6%(17/466); Long-Long 4.3% (10/230); Short-short 3.0% (7/236) Final analysis: Overall - 3.1% (35/1114); Long-long - 4.3% (18/419, Long-short -2.9% (10/350), Short-long 2.0% (7/345)
Participants	1437 women recruited from 27 sites in Thailand and enrolled from June 1997 to December 1999. Inclusion criteria: HIV-1 positive women who presented before 26 weeks gestation and who agreed not to breastfeed. Exclusion criteria: contraindication for ZDV, haemaglobin < 8g/dl. neurophil count <750/mm3, serum alanine aminotransferase level >5 x ULN and creatinine more than 1.5mg/dl, oligohydramnios, unexplained hydramnios, in utero anaemia.
Interventions	ZDV arms: Long-long - MOTHER - Oral zidovudine 300mg twice daily antenatally from 28 weeks gestation then 300mg at start of labour and 300mg every 3 hours until delivery; INFANT - Oral ZDV 2mg/kg orally every 6 hours from birth to 6 weeks Long-short - as for long-long but with infants receiving ZDV only for 3 days after birth Short-long - as for long-long but with mothers receiving ZDV from 35 weeks gestation Short-short - as for long-long but with mothers receiving ZDV from 35 weeks and infants receiving ZDV up to 3 days after birth A placebo was used to ensure blinding to treatment regimen.
Outcomes	Primary: HIV infection in infants by HIV-1 DNA PCR assessed at 1, 45, 120 and 180 days. Positive if PCR positive on 2 separate occasions
Notes	No breastfeeding. The study was approved by the ethics committees of the Thai Ministry of Public Health and the Harvard School of Public Health. Women gave written informed consent. All infants received trimethoprim-sulphamethoxazole from the age of 6 weeks until their HIV status was confirmed. After the first interim analysis on 4 December 1998 the short-short arm of the study was discontinued - 236 women had been assigned to this arm before this date with a further 87 assigned thereafter.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**PHPT-1 a**
Methods	
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	A – Adequate

Study	**PHPT-1 b**
Methods	
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	A – Adequate

Study	**PHPT-2**
Methods	Generation of allocation sequence: Unclear - randomised in permuted blocks of 6 in the ratio 1:1:1. Allocation concealment: Adequate - centrally prepared treatment packs identified by random numbers. Blinding: Participants - Yes; Providers- Yes; Assessors - Yes. Exclusions: At first interim analysis (2 May 2002): Overall 43.9% (810/1844) JV TO WRITE TO AUTHORS FOR BREAKDOWN DATA Final analysis: Overall - 26% (479/1844)
Participants	23,273 women were screened, 1,797 were randomised of which 1,457 gave birth before 18 February 1998. Participants recruited from four large public hospitals and one missionary hospital in South Africa, Tanzania and Uganda and enrolled from June 1996 to January 2000. Enrollment in the placebo arm was disontinued in February 1998. Inclusion criteria: HIV-1 +ve women with gestational age <36 weeks, age > 18 years or legal age of consent, Hb>8g/L and 18 months follow up possible. Exclusion criteria: No severe fetal abnormalities or life threatening disease and Hb
Interventions	NVP-NVP arm: MOTHERS - NVP as a single 200mg dose orally at onset of labour. INFANTS - NVP oral suspension as a single fixed dose (6mg in 0.6 ml) 48 to 72 hours after birth. NVP-PLAC arm: MOTHERS - as for NVP-NVP arm. INFANTS - Placebo 48 to 72 hours after birth PLAC-PLAC arm: MOTHERS and INFANTS given placebo only
Outcomes	Primary: Infant HIV+ by PCR on two separate occasions. Adverse events in mothers and infants
Notes	All women received ZDV 300mg twice daily from 28 weeks or later and 300mg 3 hourly from onset of labour to delivery. All infants received ZDV 2mg/kg body weight 6 hourly for 1 week after birth or for 4-6 weeks if mother received ZDV for <4 weeks. Treatment for opportunisitic infections provided as needed. No breastfeeding. The study was approved by the ethics committees of the Thai Ministry of Public Health and the Harvard School of Public Health. Women gave written informed consent. Enrolment in the PLAC-PLAC arm was stopped by the DSMB at the first interim analysis on 2 May 2002.

Characteristics of included studies (*Continued*)

Allocation concealment	A – Adequate

Study	**RETRO-CI**
Methods	Generation of allocation sequence: Unclear - Block randomisation list generated centrally. Allocation concealment: Adequate - prepared at study pharmacy; in blister packs and delivered to site. Blinding: Participants - Yes; Providers- Yes; Assessors - Unclear Exclusions: Overall - 7.5%(21/280); ZDV - 7.1% (10/140), PLAC -7.9% (11/140)
Participants	983 screened and 280 women enrolled in a single public clinic in Abijan, Cote d'Ivoire between April 1996 and February 1998. Inclusion criteria: HIV-1 positive women at 36 weeks gestation who were 18+ years old, lived in Abidjan and met laboratory criteria (Hb>70g/L, neutrophil count >1 x109 /L, platelet count >100x109/L, serum ALT <2.5XULN serum creatinine <150g/L. Exclusion criteria: HIV-2 or both HIV-1 and HIV-2 positive, previous antiretroviral therapy, medical or obstetric complications not related to HIV-1 infection increasing the risk of early maternal or fetal death.
Interventions	ZDV arm: MOTHER - Oral zidovudine 300mg twice daily from 36 weeks gestation until onset of labour, 300mg at onset of labour then 300mg every 3 hours until delivery. INFANT - no treatment PLAC arm: Identical placebo
Outcomes	HIV infection in the infant assessed by HIV-1 DNA PCR at 3 months HIV infection in the infant at 24 months Adverse events in mothers and infants
Notes	All infants BREASTFED All women gave informed consent (method not reported). The study was stopped by the DSMB early (on 18 February 1998) because safety and efficacy of ZDV had been demonstrated in a trial in Thailand. Study approved by IRB of CDC and Ethics Committee of the Cote d'Ivoire Ministry of Health.
Allocation concealment	A – Adequate

Study	**SAINT**
Methods	Generation of allocation sequence: Adequate - computer randomised scratch card sheets Permuted blocks of 4 in 2:2 ratio. Allocation concealment: Unclear - 'unknown to investigator until mother prepared to begin treatment' Blinding: Participants - No; Providers- No; Assessors - Yes Exclusions: Overall - 28.4.0% (375/1319); NVP - 28.9% (190/657), ZDV-3TC -27.9% (185/662) [Numbers taken from figure 1]
Participants	1319 women enrolled in 11 public hospitals in South Africa between May 1999 to February 2000. Inclusion criteria: HIV-1 positive, ARV naive women 16 years and older who either >38 week gestation or >35 weeks and in labour. Exclusion criteria: Elective caesarian section, presented with life threatening complications.
Interventions	NVP arm: MOTHERS - NVP as a 200mg dose orally in labour followed by a 200mg dose 48 hours later if still in labour and 200mg 24-48 hours postpartum . INFANTS - NVP oral suspension as a single 6mg dose

	24 to 48 after delivery. If infant born within 2 hours of maternal dose given in labour then given another 6mg dose within 6 hours of delivery. ZDV-3TC arm: MOTHERS - Loading dose of ZDV 600mg plus 3TC 150mg orally then ZDV 300mg every 3 hours and 3TC 150mg every 12 hours until delivery. After delivery ZDV 300mg plus 3TC 150mg twice daily for 1 week. INFANTS - commenced treatment at least 12 hours after delivery and continued for 1 week. If weight >2kg infants receive ZDV syrup 12mg BD plus 3TC BD oral solution 3mg. Weight <2kg infants received ZDV 4mg/kg and 3TC 2mg/kg. Infants born within 2 hours of first maternal dose started treatment within 6 hours after delivery.
Outcomes	Primary: HIV-1 in infants assessed by PCR DNA or RNA assay at birth and 8 weeks Adverse events in mother and baby
Notes	>40% of infants breastfed. Mothers were asked to do exclusive breastfeeding.
Allocation concealment	B – Unclear

Study	**Taha 2003**
Methods	Generation of allocation sequence: Adequate - Computer generated blocks of 10 in a 1:1 ratio, stratified by clinic. Allocation concealment: Adequate - Sequentially numbered, opaque, sealed envelopes opened after consent given. Blinding: Participant - No; Provider - No; Assessor - Yes Exclusions: Overall - 22.7% (254/1119); NVP/ZDV arm - 20.9% (118/562); NVP arm - 24.4% (136/557)
Participants	12, 355 women were screened at six antenatal clinics in Blantrye, Malawi and 1119 women were enrolled between April 2000 and January 2002. and 1119 infants were randomised. Inclusion criteria (mothers): HIV +ve women in advanced labour (as defined by cervical dilatation > 6cm; 2nd stage of labour; strong, regular contractions; estimated delivery within 2 hours after arrival) or women who delivered immediately post arrival prior to vaginal examination. Mothers did not receive NVP. Exclusion criteria (mothers): HIV -ve; women who attended antenatal clinics or who were not attenders, but arrived early at labour ward. Inclusion criteria (infants): Mothers HIV +ve; Singleton; Term
Interventions	NVP arm: INFANTS - Nevirapine 2mg/kg given orally to infant immediately after birth NVP/AZT arm: INFANTS - Nevirapine 2mg/kg given orally to infant immediately after birth AND Zidovudine 4mg/kg twice daily given orally to infant for 7 days after birth
Outcomes	Primary outcome: HIV infection at 6-8 weeks after birth in infants who were HIV-ve at birth Secondary outcomes: HIV infection at 6-8 weeks after birth in all infants including HIV+ve at birth (HIV-1 RNA assay) HIV infection at 6-8 weeks after birth for all infants tested at 6-8 weeks but excluding those tested at birth if not also tested at 6-8 weeks Death up until 1 year after birth Adverse events: Any adverse events classified as Grade 1 - 4 on the Adverse Event Toxicity Scale
Notes	99% INFANTS BREASTFED Ethics approval received from the Malawi College of Medicine Research Committee and the Johns Hopkins Bloomberg School of Public Health Committee on Human Research. All women gave written informed consent.

	The trial was stopped by the Data and Safety Monitoring Board at the second interim analysis after results were available for 809 babies. The DSMB recommended that those babies enrolled but not yet with results at 6-8 weeks continue to be assessed and included in the final analysis (222 babies).
Allocation concealment	A – Adequate

Study	**Taha 2004**
Methods	Generation of allocation sequence: Adequate - Computer generated blocks of 10 in a 1:1 ratio, stratified by clinic. Allocation concealment: Adequate - Sequentially numbered, opaque, sealed envelopes opened after consent given. Blinding: Participant - No; Provider - No; Assessor - Yes Exclusions: Overall - 10.9% (97/894); NVP/AZT arm - 8.5% (38/446); NVP arm - 13.2% (59/448)
Participants	9469 women were screened at 6 clinics in Blantrye, Malawi and enrolled between April 2000 and March 2003 and and 894 infants were randomised. Inclusion criteria (mothers): HIV +ve women presenting in early labour - four or more hours after arrival so that NVP 200 mg single oral dose could be given at 2 hrs before delivery. Exclusion criteria (mothers): Received NVP prior to delivery Inclusion criteria (infants): Not anaemic (Hb <10 g/dL), preterm, or requiring admission to intensive care unit.
Interventions	NVP arm: INFANTS: Nevirapine 2mg/kg single oral dose at birth NVP/AZT arm: INFANTS: Nevirapine 2mg/kg single oral dose at birth AND Zidovudine 4mg/kg twice daily orally for 7 days after birth Co-interventions - INFANTS: Cotrimoxazole prophylaxis up to months after birth
Outcomes	Primary outcome: HIV infection at 6-8 weeks after birth (HIV-1 RNA assay) Secondary outcomes: HIV infection at birth HIV infection at 6-8 weeks after birth in those not infected at birth Infant deaths at 6-8 weeks Adverse events: Grade 3 and 4 events on the Adverse Event Toxicity Scale
Notes	99% INFANTS BREASTFED Ethics approval received from the Malawi College of Medicine Research and Ethics Committee and the Johns Hopkins Bloomberg School of Public Health Committee on Human Research. All women gave written informed consent.
Allocation concealment	A – Adequate

Study	**Thai-CDC**
Methods	Generation of allocation sequence: Adequate - Computer generated blocks randomly varying in size between 4 and 6. Allocation concealment: Adequate - Investigators not involved in sequence generation. Treatment allocation concealed from investigators by sequentially numbered drug packs.

	Blinding: Participant - Yes; Provider - Yes; Assessor - Yes Exclusions: Overall - 1.2% (5/397); ZDV arm - 2.0% (4/198); Placebo arm - 0.5% (1/199)
Participants	1140 women from two hospitals in Bangkok, Thailand were screened, 423 were enrolled between May 1996 to December 1997 of which 397 were randomised. Inclusion criteria: Women who were HIV-1 +ve within 28 days before randomisation, were > 18 years at <= 34 weeks gestation, lived in or near study area, intended to deliver at the study hospital, did not intend to breastfeed and met laboratory criteria: haemoglobin >80g/L, neutrophils 1.0 x 10^9/L, alanine aminotransferase 2.5x or less ULN, serum creatinine 133 micromol/L or less and urine protein 150mg/day or less by dipstick test (<=1+). Exclusion criteria: Intolerance to ZDV, used ARVs or had amniocentesis in current pregnancy, preexisting fetal abnormalities.
Interventions	MOTHERS: Oral zidovudine 300mg twice daily from 36 weeks until onset of labour and taken once at onset of labour and then 300mg every 3 hours until delivery or matching placebo. INFANTS: none
Outcomes	Primary: HIV-1 infection at birth, 2 months and 6 months (HIV-1 DNA PCR testing) Secondary: Adverse events up to 18 months
Notes	NO INFANT BREASTFED Ethics approval received from the Ministry of Public Health, Thailand and Centres for Disease Control and Prevention, USA. All women gave written informed consent.
Allocation concealment	A – Adequate

Study	**Thistle 2004**
Methods	Generation of allocation sequence: Adequate - Computer generated block randomisation. Allocation concealment: Adequate - Allocation schedule prepared by off site statistician and provided in 'ordered opaque envelopes.' Blinding: Participant - Yes; Provider - Yes; Assessor - Unsure Exclusions: Overall - 19.4% (43/222). 8 of 222 maternal specimens were lost. As it is not known how these were distributed between the comparison groups the exclusion rate per group could not be calculated.
Participants	222 women randomised August 1999 and December 2000 at a rural hospital in Zimbabwe. Inclusion criteria: HIV +ve women presenting in early before 35 weeks gestation.
Interventions	"Thai Regimen": MOTHERS- ZDV 300mg po twice daily from 36 weeks to labour then ZDV 300mg po 3 hourly until delivery. INFANTS - Placebo "Ultrashort Regimen" MOTHERS - Placebo from 36 weeks to labour then ZDV 300mg po 3 hourly until delivery. INFANTS - ZDV suspension 2mg/kg po 4 times daily for first 3 days of life.
Outcomes	Primary outcome: HIV infection in infants 6 weeks after birth (HIV-1 RNA assay) Other outcomes: Cumulative death rate in infants at 6 weeks, 3 months, 6 months and 1 year. Maternal death and serious adverse effects
Notes	ZDV suspension prepared in the hospital by dissolving 100mg capsules in 30 ml sterile water. "Women were counselled to undertake early and rapid weaning at 5 months."

	Ethics approval received from the Medical Research Council of Zimbabwe and the IRB of Lakeridge Health Corp., Canada. Women gave written informed consent.
Allocation concealment	A – Adequate

ULN = upper limit normal
IRBs = institutional review board

Characteristics of excluded studies

Study	Reason for exclusion
El Beitune 2005	This is a prospective cohort study and is not randomized
Leroy 2002	This is a pooled analysis of the individual data from two trials already included in the review viz. DITRAME and RETRO-CI
Leroy 2005	This is a pooled analysis of the individual data from five trials of breast-feeding populations already included in the review viz. DITRAME, RETRO-CI, PETRA, SAINT and HIVNET 012
Shetty 2003	This safety trial randomised infants of HIV+ve mothers at 2 study sites (South Africa and Zimbabwe) to once weekly, twice weekly or once daily NVP for 24 weeks and assessed the safety and trough concentrations of the drug. It reported on the HIV status for infants only from the site in Zimbabwe after sample collection as processing deficiencies were identified at the South African site
Yoshimoto 2005	This is a prospective cohort study and is not randomized (translated from the Portuguese)

Characteristics of ongoing studies

Study	BAN 2005
Trial name or title	BAN (registered on www.clinicaltrials.gov with ID: NCT00164736) The Breastfeeding, Antiretroviral, and Nutrition (BAN) study. The trial is based at Kamuzu Central Hospital, Lilongwe, Malawi. A Prevention, Randomized, Open Label, Placebo Control, Factorial Assignment, Safety/ Efficacy Study.
Participants	PRIMARY ELIGIBILITY CRITERIA: Age >14 years. Ability to give informed assent or consent. Evidence of HIV infection, as documented by 2 positive ELISA's; or 1 positive ELISA, and 1 WB; or 2 separate concurrent rapid tests. Currently pregnant (with a single or multiple fetuses). Intention to breastfeed. Gestation < 30 weeks at referral from CTA. No serious current complications of pregnancy. Intention to deliver at the institution at which the study is based.Not previously enrolled in this study for an earlier pregnancy. Other than HIV, no active serious infection, such as tuberculosis or other potentially serious illnesses. No previous use of antiretrovirals including the HIVNET 012 regimen. Mother's CD4 count > 200 cells/uL determined in the antenatal clinic. Mother's ALT < 2.5 x ULN determined in the antenatal clinic. SECONDARY ELIGIBILTY CRITERIA: Mother who delivers outside of the institution at which the study is based must present with her infant to the study site within 36 hours of delivery. Mother accepts nevirapine and ZDV+3TC 7-day regimen for herself and her infant. Infant birthweight > 2000 g. No severe congenital malformations or other condition(s) not compatible with life. Based on clinical assessment, no maternal condition which would preclude start of study intervention.
Interventions	The study will evaluate the following: 1) The efficacy of a high-density caloric/micronutrient nutritional supplement given to HIV-infected women who breastfeed in preventing maternal depletion (weight loss and micronutrient status). 2) The safety and efficacy of maternal or infant antiretroviral regimens, taken for up to 6 months during breastfeeding, in reducing infant HIV infection rates at 48 weeks. 3) The feasibility of exclusive breastfeeding for 6 months followed by rapid weaning. Additional study objectives are to evaluate the feasibility of delivering these interventions in resource poor settings and to identify maternal, infant, and virologic factors

Characteristics of ongoing studies (*Continued*)

	associated with HIV transmission during breastfeeding. Drug: Maternal Zidovudine/Lamivudine/Lopinavir-Ritonavir; Drug: Infant nevirapine; Drug: Maternal protein and calorie supplement.
Outcomes	PRIMARY OUTCOMES: 1. Postpartum weight loss between delivery and 28 weeks.; 2. Infant HIV status at 28 weeks. (Infants found to have HIV at birth or 2 weeks after delivery will have been disenrolled.); 3. Exclusive breastfeeding and breastfeeding cessation by 28 weeks.
Starting date	Study start: March 2004; Expected completion: March 2010. Last follow-up: September 2009; Data entry closure: December 2009. In July 2006, 847 mother-infant pairs have been assigned treatment out of a planned 2,418 (35%)
Contact information	Charles van der Horst. Email: cvdh@med.unc.edu
Notes	

Study	**SIMBA**
Trial name or title	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

d4T = stavudine, ddI = didanosine, ZDV = zidovudine, 3TC = lamivudine, NVP = nevirapine

ADDITIONAL TABLES

Table 01. Search strategy for MEDLINE

Number	Search terms
#1	HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw]))
#2	Antiretroviral Therapy, Highly Active[MeSH] OR Anti-Retroviral Agents[MeSH] OR Antiviral Agents[MeSH:NoExp] OR ((anti) AND (hiv[tw])) OR antiretroviral*[tw] OR ((anti) AND (retroviral*[tw])) OR HAART[tw] OR ((anti) AND (acquired immunodeficiency[tw])) OR ((anti) AND (acquired immunedeficiency[tw])) OR ((anti) AND (acquired immuno-deficiency[tw])) OR ((anti) AND (acquired immune-deficiency[tw])) OR ((anti) AND (acquired immun*) AND (deficiency[tw])) OR NEVIRAPINE OR ZIDOVUDINE OR LAMIVUDINE
#3	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])
#4	(MOTHER-TO-CHILD TRANSMISSION)
#5	MTCT

Table 01. Search strategy for MEDLINE (*Continued*)

Number	Search terms
#6	(DISEASE TRANSMISSION, VERTICAL)
#7	#4 OR #5 OR #6
#8	#1 AND #2 AND #3 AND #7

Table 02. Search strategy for EMBASE

Number	Search terms
#1	'human immunodeficiency virus infection'/exp
#2	'human immunodeficiency virus'/exp
#3	hiv:ti OR hiv:ab
#4	'hiv-1':ti OR 'hiv-1':ab
#5	'hiv-2':ti OR 'hiv-2':ab
#6	'human immunodeficiency virus':ti OR 'human immuno deficiency':ab
#7	'human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab
#8	'human immunedeficiency virus':ti OR 'human immune deficiency virus':ab
#9	'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab
#10	'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab
#11	'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab
#12	'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab
#13	'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	'anti human immunedeficiency':ti OR 'anti human immunedeficiency':ab
#16	'anti human immune-deficiency':ti OR 'anti human immune-deficiency':ab
#17	'anti human immunodeficiency':ti OR 'anti human immunodeficiency':ab
#18	'anti human immuno-deficiency':ti OR 'anti human immuno-deficiency':ab
#19	'anti acquired immuno-deficiency':ti OR 'anti acquired immuno-deficiency':ab
#20	'anti acquired immunodeficiency':ti OR 'anti acquired immunodeficiency':ab
#21	'anti acquired immunedeficiency':ti OR 'anti acquired immunedeficiency':ab
#22	'anti acquired immune-deficiency':ti OR 'anti acquired immune-deficiency':ab
#23	'anti hiv':ti OR 'anti hiv':ab
#24	antiretrovir*:ti OR antiretrovir*:ab
#25	'anti retroviral':ti OR 'anti retroviral':ab OR 'anti retrovirals':ti OR 'anti retrovirals':ab OR 'anti retrovirus':ti OR 'anti

Table 02. Search strategy for EMBASE (*Continued*)

Number	Search terms
	retrovirus':ab
#26	haart:ti OR haart:ab
#27	'anti human immunodeficiency virus agent'/de
#28	'antiretrovirus agent'/de
#29	'antivirus agent'/de
#30	'highly active antiretroviral therapy'/de
#31	'zidovudine'/de
#32	'nevirapine'/de
#33	'lamivudine'/de
#34	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR # 22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
#35	'mother-to-child transmission'
#36	mtct
#37	'disease transmission, vertical'/de
#38	#35 OR #36 OR #37
#39	random*:ti OR random*:ab
#40	factorial*:ti OR factorial*:ab
#41	cross?over*:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab
#42	placebo*:ti OR placebo*:ab
#43	((doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab))
#44	((singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab))
#45	assign*:ti OR assign*:ab
#46	volunteer*:ti OR volunteer*:ab
#47	'crossover procedure'/de
#48	'double-blind procedure'/de
#49	'single-blind procedure'/de
#50	'randomized controlled trial'/de
#51	allocat*:ti OR allocat*:ab
#52	#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51
#53	#14 AND #34 AND #38 AND #52

Table 03. Search strategy for AIDSearch

Number	Search terms
#1	PT=RANDOMIZED CONTROLLED TRIAL
#2	PT=CONTROLLED CLINICAL TRIAL
#3	RANDOMIZED CONTROLLED TRIALS
#4	RANDOM ALLOCATION
#5	DOUBLE BLIND METHOD
#6	SINGLE BLIND METHOD
#7	PT=CLINICAL TRIAL
#8	CLINICAL TRIALS OR CLINICAL TRIALS, PHASE I OR CLINICAL TRIALS, PHASE II OR CLINICAL TRIALS, PHASE III OR CLINICAL TRIALS, PHASE IV OR CONTROLLED CLINICAL TRIALS OR MULTICENTER STUDIES
#9	(SINGL* OR DOUBL* OR TREBL* OR TRIPL*) NEAR6 (BLIND* OR MASK*)
#10	CLIN* NEAR6 TRIAL*
#11	PLACEBO*
#12	PLACEBOS
#13	RANDOM*
#14	RESEARCH DESIGN
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	ANIMALS NOT (HUMAN AND ANIMALS)
#17	#15 NOT #16
#18	ZIDOVUDINE
#19	LAMIVUDINE
#20	NEVIRAPINE
#21	#18 OR #19 OR #20
#22	MTCT
#23	(MOTHER-TO-CHILD TRANSMISSION)
#24	(DISEASE TRANSMISSION, VERTICAL)
#25	#22 OR #23 OR #24
#26	#17 AND #21 AND #25

Table 04. Search strategy for CENTRAL

#1	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUN* DEFICIENCY VIRUS) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME) OR (ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUN* DEFICIENCY SYNDROME) in All Fields in all products
#2	MeSH descriptor HIV Infections explode all trees in MeSH products
#3	MeSH descriptor HIV explode all trees in MeSH products
#4	(#1 OR #2 OR #3)
#5	MeSH descriptor Antiretroviral Therapy, Highly Active, this term only in MeSH products
#6	MeSH descriptor Anti-HIV Agents explode all trees in MeSH products
#7	MeSH descriptor Antiviral Agents, this term only in MeSH products
#8	ANTI HIV in All Fields in all products
#9	ANTIRETROVIRAL* OR (ANTI RETROVIRAL*) in All Fields in all products
#10	LAMIVUDINE OR NEVIRAPINE OR ZIDOVUDINE in All Fields in all products
#11	(MOTHER-TO-CHILD TRANSMISSION) OR MTCT OR (DISEASE TRANSMISSION, VERTICAL) in All Fields in all products
#12	(#5 OR #6 OR #7 OR #8 OR #9 OR #10)
#13	(#4 AND #11 AND #12)

ANALYSES

Comparison 01. Antiretrovirals versus Placebo.

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 HIV infection at birth			efficacy (%) (Random) 95% CI	Totals not selected
02 HIV infection at 4 to 8 weeks.			efficacy (%) (Random) 95% CI	Totals not selected
03 HIV infection at 3 to 4 months.			efficacy (%) (Random) 95% CI	Totals not selected
04 HIV infection at 6 months			efficacy (%) (Random) 95% CI	Totals not selected
05 HIV infection at 12 months			efficacy (%) (Random) 95% CI	Totals not selected
06 HIV infection at 18 months			efficacy (%) (Random) 95% CI	Totals not selected
07 HIV infection or death at 4 to 8 weeks.			efficacy (%) (Random) 95% CI	Totals not selected
11 HIV infection or death at 18 months.			efficacy (%) (Random) 95% CI	Totals not selected
12 Number of infants dying during first 8 days of life.			Relative Risk (Random) 95% CI	Totals not selected
13 Number of infants dying during first 4 to 8 weeks of life			Relative Risk (Random) 95% CI	Totals not selected
14 Number of infants dying during first 3 to 4 months of life			Relative Risk (Random) 95% CI	Totals not selected
15 Number of infants dying during first 6 months of life			Relative Risk (Random) 95% CI	Totals not selected
16 Number of infants dying during first 12 months of life			Relative Risk (Random) 95% CI	Totals not selected
17 Number of infants dying during first 18 months of life			Relative Risk (Random) 95% CI	Totals not selected
19 Number of premature babies based on author's definition			Relative Risk (Random) 95% CI	Totals not selected
20 Number of babies weighing less than 2.5kg.			Relative Risk (Random) 95% CI	Totals not selected
21 Stillbirth rates			Relative Risk (Random) 95% CI	Totals not selected

Comparison 02. Longer versus shorter regimens using the same ARVs.

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 HIV infection at birth			efficacy (%) (Random) 95% CI	Totals not selected
02 HIV infection at 4 to 8 weeks.			efficacy (%) (Random) 95% CI	Totals not selected
03 HIV infection at 3 to 4 months.			efficacy (%) (Random) 95% CI	Totals not selected
04 HIV infection at 6 months			efficacy (%) (Random) 95% CI	Totals not selected
05 HIV infection at 12 months			efficacy (%) (Random) 95% CI	Totals not selected
09 HIV infection or death at 6 months.			efficacy (%) (Random) 95% CI	Totals not selected
13 Number of infants dying during first 4 to 8 weeks of life			Relative Risk (Random) 95% CI	Totals not selected
14 Number of infants dying during first 3 to 4 months of life			Relative Risk (Random) 95% CI	Totals not selected

15 Number of infants dying during first 6 months of life	Relative Risk (Random) 95% CI	Totals not selected
16 Number of infants dying during first 12 months of life	Relative Risk (Random) 95% CI	Totals not selected
19 Number of premature babies based on author's definition	Relative Risk (Random) 95% CI	Totals not selected
20 Number of babies weighing less than 2.5kg.	Relative Risk (Random) 95% CI	Totals not selected
21 Stillbirth rates	Relative Risk (Random) 95% CI	Totals not selected

Comparison 03. Regimens using different ARVs and durations of treatment.

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 HIV infection at birth			efficacy (%) (Random) 95% CI	Totals not selected
02 HIV infection at 4 to 8 weeks.			efficacy (%) (Random) 95% CI	Totals not selected
03 HIV infection at 3 to 4 months.			efficacy (%) (Random) 95% CI	Totals not selected
04 HIV infection at 6 months			efficacy (%) (Random) 95% CI	Totals not selected
05 HIV infection at 12 months			efficacy (%) (Random) 95% CI	Totals not selected
06 HIV infection at 18 months			efficacy (%) (Random) 95% CI	Totals not selected
07 HIV infection or death at 4 to 8 weeks.			efficacy (%) (Random) 95% CI	Totals not selected
08 HIV infection or death at 3 to 4 months.			efficacy (%) (Random) 95% CI	Totals not selected
10 HIV infection or death at 12 months.			efficacy (%) (Random) 95% CI	Totals not selected
11 HIV infection or death at 18 months.			efficacy (%) (Random) 95% CI	Totals not selected
12 Number of infants dying during first 8 days of life.			Relative Risk (Random) 95% CI	Totals not selected
13 Number of infants dying during first 4 to 8 weeks of life			Relative Risk (Random) 95% CI	Totals not selected
15 Number of infants dying during first 6 moths of life			Relative Risk (Random) 95% CI	Totals not selected
17 Number of infants dying during first 18 months of life			Relative Risk (Random) 95% CI	Totals not selected
19 Number of premature babies based on author's definition			Relative Risk (Random) 95% CI	Totals not selected
20 Number of babies weighing less than 2.5kg, except SAINT: <2 kg.			Relative Risk (Random) 95% CI	Totals not selected
21 Stillbirth rates			Relative Risk (Random) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-HIV Agents [*therapeutic use]; Disease Transmission, Vertical [*prevention & control]; HIV Infections [prevention & control; *transmission]; Nevirapine [therapeutic use]; Pregnancy Complications, Infectious [*drug therapy]; Randomized Controlled Trials; Reverse Transcriptase Inhibitors [*therapeutic use]; Zidovudine [therapeutic use]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection
Authors	Volmink J, Siegfried NL, van der Merwe L, Brocklehurst P
Contribution of author(s)	Information not supplied by author
Issue protocol first published	/
Review first published	1995/2
Date of most recent amendment	22 May 2007
Date of most recent SUBSTANTIVE amendment	08 November 2006
What's New	This is one of several reviews addressing the topic of mother-to-child transmission of HIV infection and supercedes the previous review: Brocklehurst P. Interventions aimed at decreasing the risk of mother-to-child transmission of HIV Infection. This review will remain on the Cochrane Library until the new protocols or reviews are published. This review was substantially changed on the 23rd March 2001. Previously all interventions aimed at decreasing the risk of mother to child transmission of HIV infection had been included in a single review. As the number of trials in this area increased, the review was split into several smaller reviews, the first of which is this review 'Antiretroviral therapy for reducing the risk of mother-to-child transmission of HIV infection'.
Date new studies sought but none found	23 March 2001
Date new studies found but not yet included/excluded	23 March 2001
Date new studies found and included/excluded	23 March 2001
Date authors' conclusions section amended	23 March 2001
Contact address	Prof Jimmy Volmink Deputy Dean: Research and SACC Director Faculty of Health Sciences Stellenbosch University PO Box 19063 Tygerberg 7505 SOUTH AFRICA E-mail: jvolmink@sun.ac.za Tel: +27 21 938 9643 Fax: +27 21 938 9558
DOI	10.1002/14651858.CD003510.pub2
Cochrane Library number	CD003510
Editorial group	Cochrane HIV/AIDS Group
Editorial group code	HM-HIV

GRAPHS AND OTHER TABLES

Figure 01. Map of the country locations of all the MTCT trials with countries where trials have taken place shaded in green.

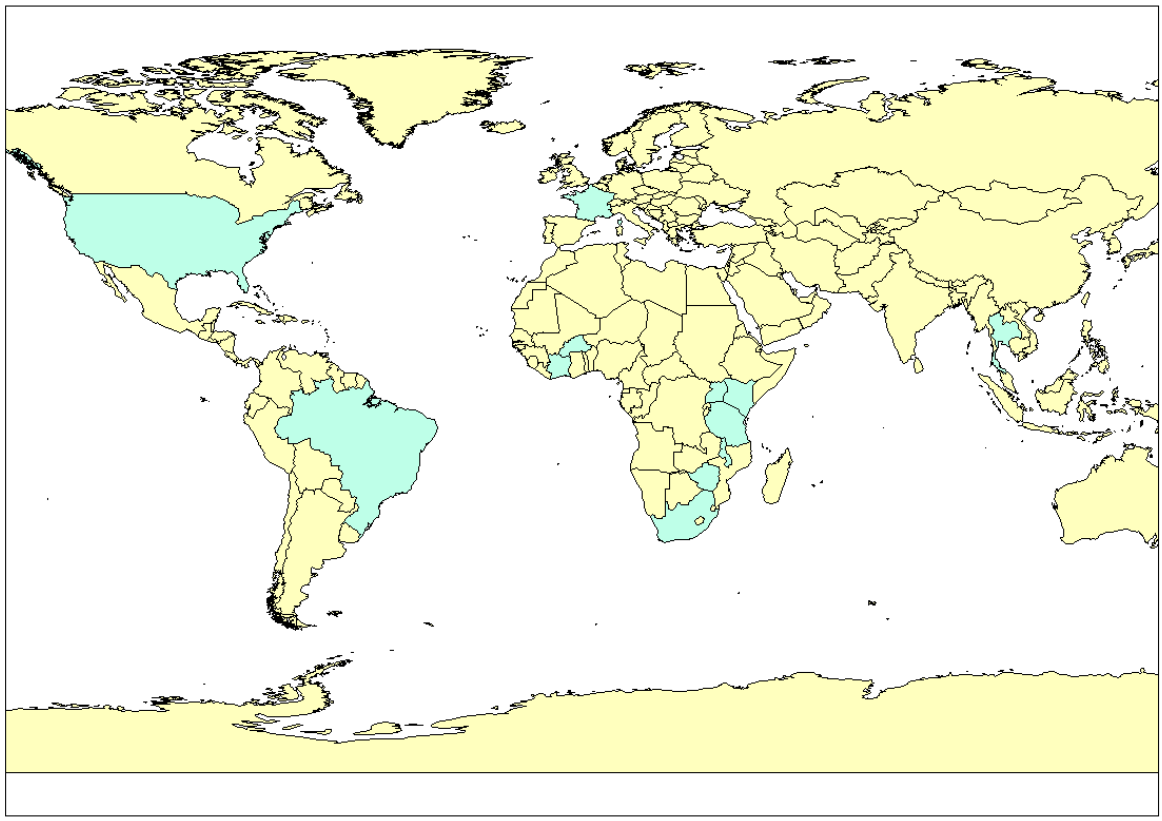


Figure 02. Exact locations of MTCT trials plotted using geogrophic co-ordinates - more than one trial can take place in a location

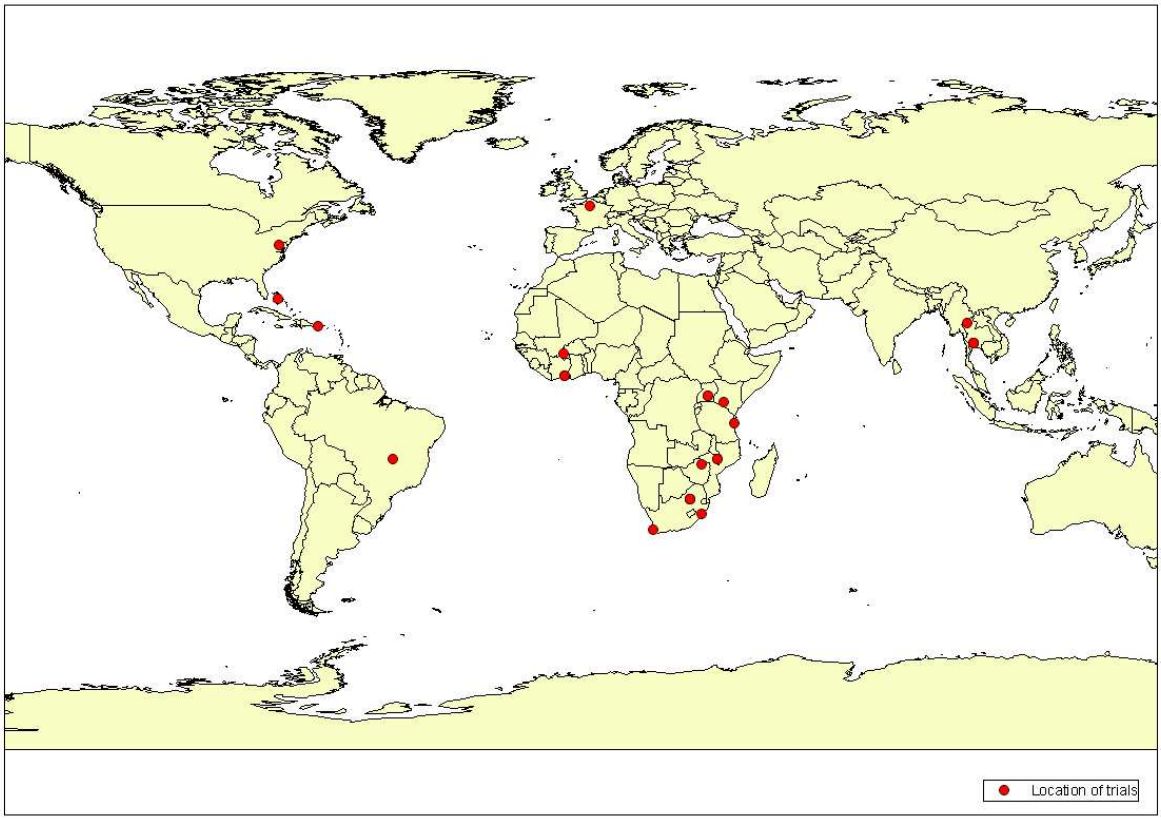


Figure 03. Exact location of the five multisite MTCT trials included in this review plotted using geographic co-ordinates

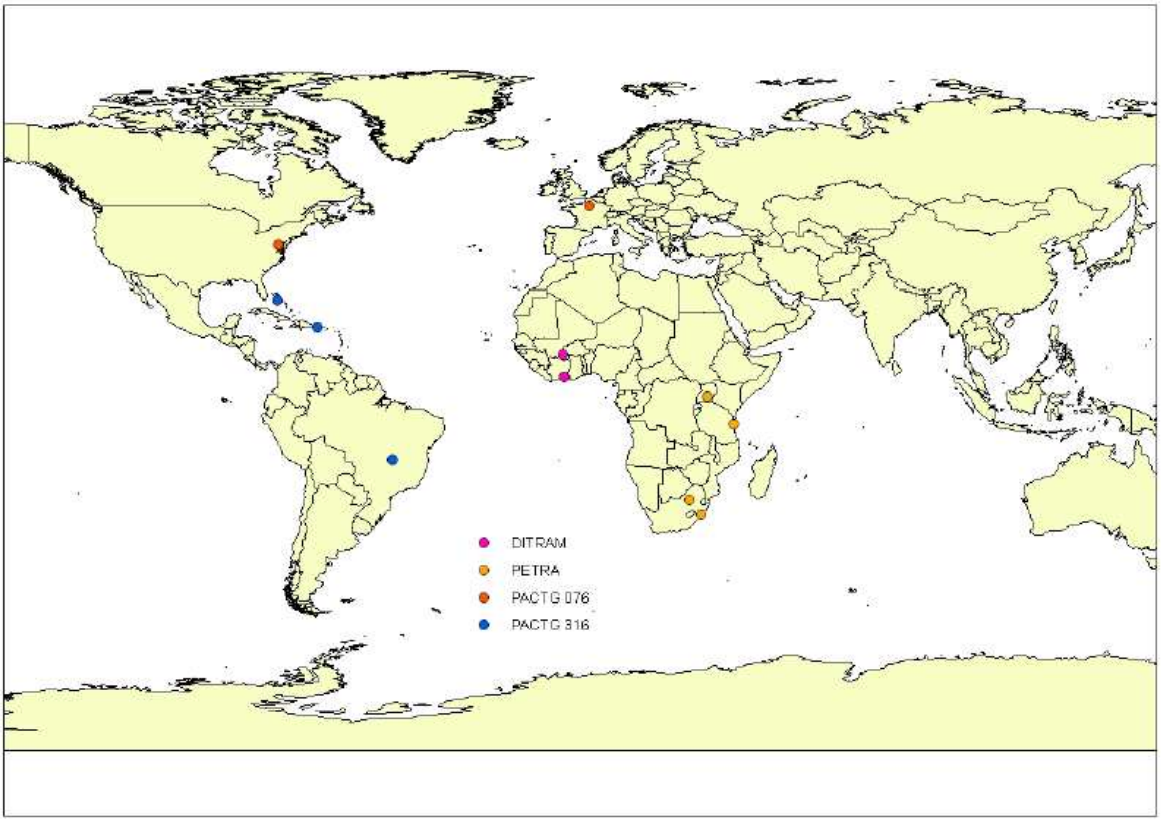


Figure 04. Exact location of the five multisite MTCT trials included in this review plotted using geographic co-ordinates

Timepoints with HIV efficacy (X) or HIV efficacy and HIV or death efficacy (XM) data reported. BF= breastfeeding population														
		Number of months												
NAME	BF	0	0.25	0.5	1	1.5	2	3	4	6	9	12	18	Points
DITRAME	yes		X			X		X		X	X	X	X	7
RETRO	yes	X			X			X	X					4
PETRA*	yes					XM							XM	2
HIVNET012	yes		XM				XM		XM			XM	XM	5
Thistle2004	yes	X		X		X		X		X		X		6
Taha2003	yes	n/a					X							2
Taha2004	yes	n/a					X							2
Bhoopat2005	no	X							X					2
PACTG076	no												X	1
Limpongsanurak2001	no									X				1
THAI-CDC	no						X							1
PACTG316	no						X							1
PHPT-1*	no									XM				1
Gray2006*	no	X				X		X		X				4
SAINT	no						XM							1
Kiarie2003	no					X								1
Gray2005	no	n/a	n/a			X		X						4
PHPT-2	no	X								XM				2
Number of trials		15	3	1	1	6	6	5	3	6	1	3	4	

Analysis 01.01. Comparison 01 Antiretrovirals versus Placebo., Outcome 01 HIV infection at birth

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 01 HIV infection at birth

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
RETRO-CI	129	135	-14.00 (76.00)		-14.00 [-162.96, 134.96]
02 Not breastfeeding					
Thai-CDC	196	199	30.00 (37.00)		30.00 [-42.52, 102.52]

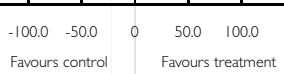
Analysis 01.02. Comparison 01 Antiretrovirals versus Placebo., Outcome 02 HIV infection at 4 to 8 weeks.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 02 HIV infection at 4 to 8 weeks.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
DITRAME	193	198	32.00 (16.00)		32.00 [0.64, 63.36]
PETRA a	467	352	63.00 (11.00)		63.00 [41.44, 84.56]
PETRA b	467	352	42.00 (15.00)		42.00 [12.60, 71.40]
PETRA c	467	352	7.00 (20.00)		7.00 [-32.20, 46.20]
RETRO-CI	129	135	44.00 (18.00)		44.00 [8.72, 79.28]
02 Not breastfeeding					
Thai-CDC	196	199	50.00 (19.00)		50.00 [12.76, 87.24]



Analysis 01.03. Comparison 01 Antiretrovirals versus Placebo., Outcome 03 HIV infection at 3 to 4 months.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 03 HIV infection at 3 to 4 months.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
DITRAME	193	198	34.00 (14.00)		34.00 [6.56, 61.44]
RETRO-CI	129	135	37.00 (17.00)		37.00 [3.68, 70.32]

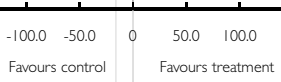
Analysis 01.04. Comparison 01 Antiretrovirals versus Placebo., Outcome 04 HIV infection at 6 months

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 04 HIV infection at 6 months

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
DITRAME	193	198	35.00 (13.00)		35.00 [9.52, 60.48]
02 Not breastfeeding					
Limpongsanurak 2001	90	92	9.00 (18.00)		9.00 [-26.28, 44.28]



Analysis 01.05. Comparison 01 Antiretrovirals versus Placebo., Outcome 05 HIV infection at 12 months

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 05 HIV infection at 12 months

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
DITRAME	193	198	34.00 (13.00)		34.00 [8.52, 59.48]

Analysis 01.06. Comparison 01 Antiretrovirals versus Placebo., Outcome 06 HIV infection at 18 months

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 06 HIV infection at 18 months

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
DITRAME	193	198	30.00 (14.00)		30.00 [2.56, 57.44]
PETRA a	467	352	33.00 (23.00)		33.00 [-12.08, 78.08]
PETRA b	467	352	18.00 (23.00)		18.00 [-27.08, 63.08]
PETRA c	468	352	10.00 (26.00)		10.00 [-40.96, 60.96]
02 Not breastfeeding					
PACTG 076	198	204	66.00 (16.00)		66.00 [34.64, 97.36]

Analysis 01.07. Comparison 01 Antiretrovirals versus Placebo., Outcome 07 HIV infection or death at 4 to 8 weeks.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 07 HIV infection or death at 4 to 8 weeks.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
PETRA a	467	352	61.00 (10.00)		61.00 [41.40, 80.60]
PETRA b	467	352	36.00 (14.00)		36.00 [8.56, 63.44]
PETRA c	468	352	3.00 (18.00)		3.00 [-32.28, 38.28]

Analysis 01.11. Comparison 01 Antiretrovirals versus Placebo., Outcome 11 HIV infection or death at 18 months.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 11 HIV infection or death at 18 months.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
PETRA a	467	352	26.00 (20.00)		26.00 [-13.20, 65.20]
PETRA b	467	352	7.00 (24.00)		7.00 [-40.04, 54.04]
PETRA c	468	352	2.00 (24.00)		2.00 [-45.04, 49.04]

Analysis 01.12. Comparison 01 Antiretrovirals versus Placebo., Outcome 12 Number of infants dying during first 8 days of life.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 12 Number of infants dying during first 8 days of life.

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
DITRAME	6/214	3/217		2.03 [0.51, 8.00]
RETRO-CI	1/140	8/140		0.13 [0.02, 0.99]

Analysis 01.13. Comparison 01 Antiretrovirals versus Placebo., Outcome 13 Number of infants dying during first 4 to 8 weeks of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 13 Number of infants dying during first 4 to 8 weeks of life

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
DITRAME	7/214	4/217		1.77 [0.53, 5.97]
PETRA a	4/475	9/377		0.35 [0.11, 1.14]
PETRA b	8/474	9/377		0.71 [0.28, 1.81]
PETRA c	11/471	9/377		0.98 [0.41, 2.34]
Thai-CDC	1/198	2/199		0.50 [0.05, 5.50]

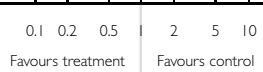
Analysis 01.14. Comparison 01 Antiretrovirals versus Placebo., Outcome 14 Number of infants dying during first 3 to 4 months of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 14 Number of infants dying during first 3 to 4 months of life

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
DITRAME	11/214	15/217		0.74 [0.35, 1.58]
RETRO-CI	3/140	20/140		0.15 [0.05, 0.49]



Analysis 01.15. Comparison 01 Antiretrovirals versus Placebo., Outcome 15 Number of infants dying during first 6 months of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 15 Number of infants dying during first 6 months of life

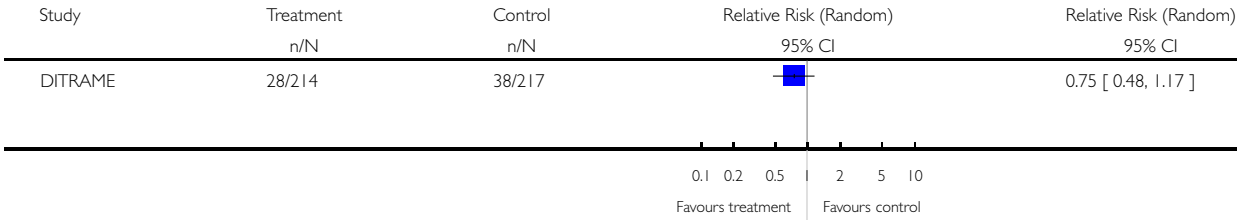
Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
DITRAME	17/214	28/217		0.62 [0.35, 1.09]

Analysis 01.16. Comparison 01 Antiretrovirals versus Placebo., Outcome 16 Number of infants dying during first 12 months of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 16 Number of infants dying during first 12 months of life

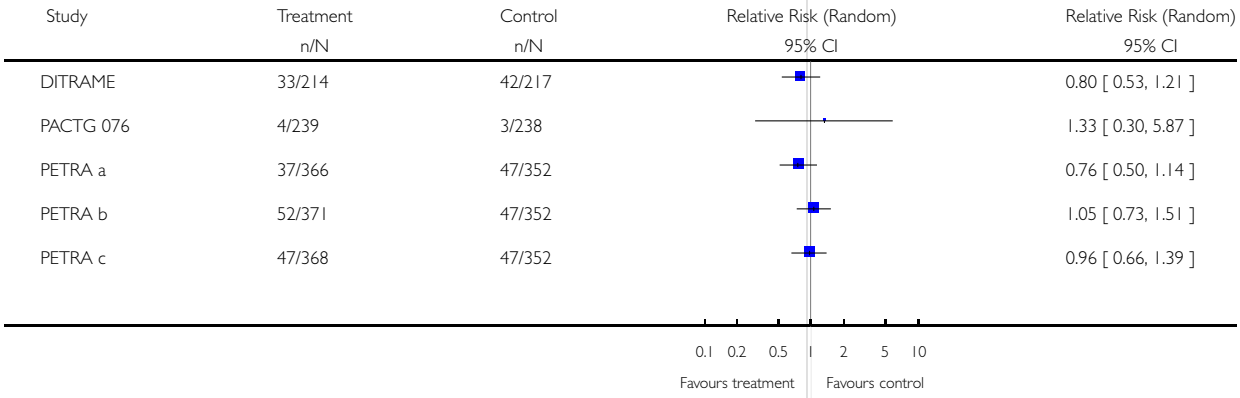


Analysis 01.17. Comparison 01 Antiretrovirals versus Placebo., Outcome 17 Number of infants dying during first 18 months of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 17 Number of infants dying during first 18 months of life

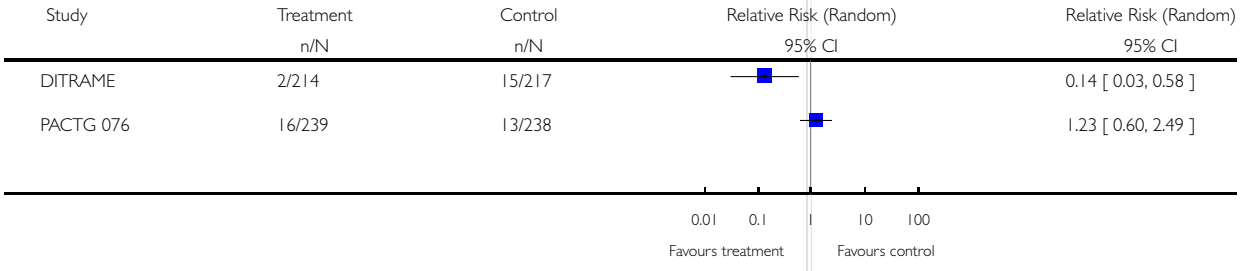


Analysis 01.19. Comparison 01 Antiretrovirals versus Placebo., Outcome 19 Number of premature babies based on author's definition

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 19 Number of premature babies based on author's definition



Analysis 01.20. Comparison 01 Antiretrovirals versus Placebo., Outcome 20 Number of babies weighing less than 2.5kg.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 20 Number of babies weighing less than 2.5kg.

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
DITRAME	28/214	31/217		0.92 [0.57, 1.47]
PACTG 076	28/239	37/238		0.75 [0.48, 1.19]
Thai-CDC	11/198	18/199		0.61 [0.30, 1.27]

Analysis 01.21. Comparison 01 Antiretrovirals versus Placebo., Outcome 21 Stillbirth rates

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 01 Antiretrovirals versus Placebo.

Outcome: 21 Stillbirth rates

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
DITRAME	1/214	7/217		0.14 [0.02, 1.17]
Limpongsanurak 2001	1/90	0/92		3.07 [0.13, 74.28]
PACTG 076	0/239	1/238		0.33 [0.01, 8.11]
PETRA a	2/475	4/377		0.40 [0.07, 2.15]
PETRA b	6/474	4/377		1.19 [0.34, 4.20]
PETRA c	4/471	4/377		0.80 [0.20, 3.18]
RETRO-CI	7/140	2/140		3.50 [0.74, 16.55]
Thai-CDC	1/198	0/199		3.02 [0.12, 73.57]

Analysis 02.01. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 01 HIV infection at birth

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 01 HIV infection at birth

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
Bhoopat 2005	23	27	100.00 (201.00)		100.00 [-293.95, 493.95]
PHPT-2	693	672	38.00 (40.00)		38.00 [-40.40, 116.40]
Thistle 2004	111	111	-15.00 (70.00)		-15.00 [-152.20, 122.20]

Analysis 02.02. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 02 HIV infection at 4 to 8 weeks.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 02 HIV infection at 4 to 8 weeks.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
Thistle 2004	111	111	17.00 (30.00)		17.00 [-41.80, 75.80]

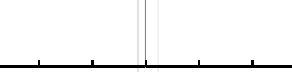
Analysis 02.03. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 03 HIV infection at 3 to 4 months.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 03 HIV infection at 3 to 4 months.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
Thistle 2004	111	111	14.00 (27.00)		14.00 [-38.92, 66.92]
02 Not breastfeeding					
Bhoopat 2005	23	27	100.00 (58.00)		100.00 [-13.68, 213.68]



Analysis 02.04. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 04 HIV infection at 6 months

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 04 HIV infection at 6 months

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
Thistle 2004	111	111	8.00 (26.00)		8.00 [-42.96, 58.96]
02 Not breastfeeding					
PHPT-1 a	401	338	24.00 (23.00)		24.00 [-21.08, 69.08]
PHPT-1 b	340	338	45.00 (22.00)		45.00 [1.88, 88.12]
PHPT-2	693	672	29.00 (28.00)		29.00 [-25.88, 83.88]

Analysis 02.05. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 05 HIV infection at 12 months

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 05 HIV infection at 12 months

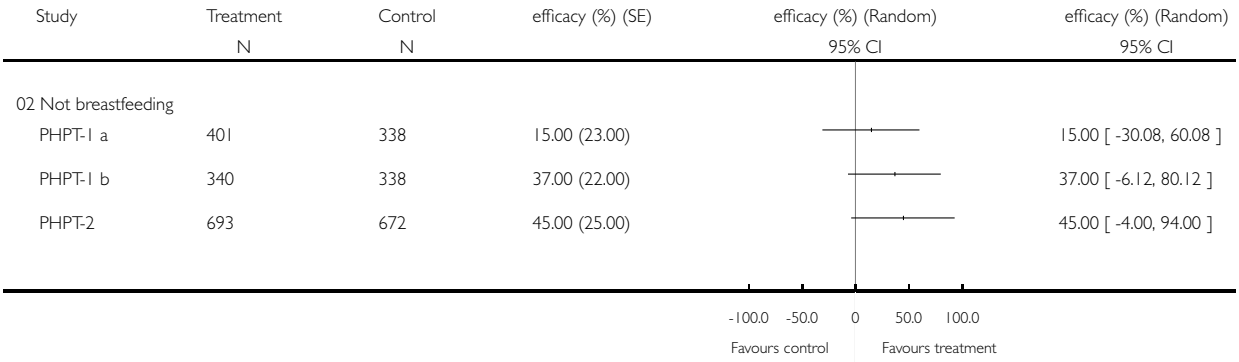
Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
Thistle 2004	111	111	9.00 (22.00)		9.00 [-34.12, 52.12]

Analysis 02.09. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 09 HIV infection or death at 6 months.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 09 HIV infection or death at 6 months.

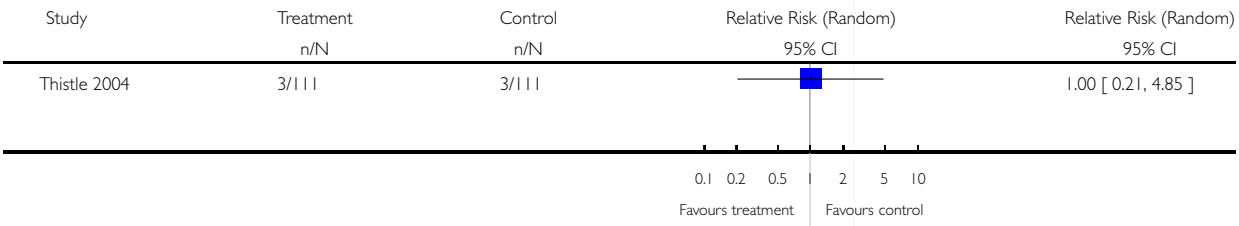


Analysis 02.13. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 13 Number of infants dying during first 4 to 8 weeks of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 13 Number of infants dying during first 4 to 8 weeks of life

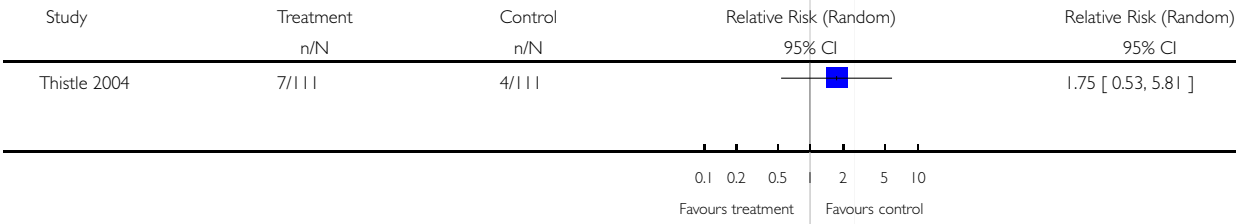


Analysis 02.14. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 14 Number of infants dying during first 3 to 4 months of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 14 Number of infants dying during first 3 to 4 months of life

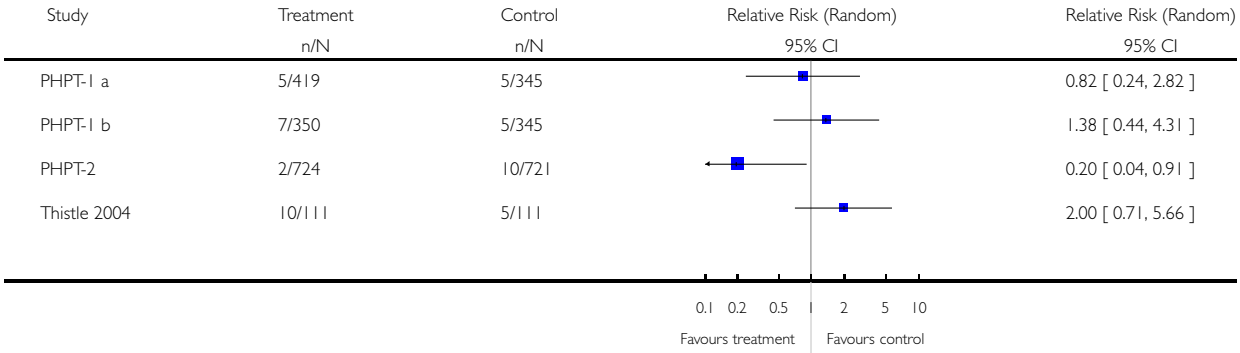


Analysis 02.15. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 15 Number of infants dying during first 6 months of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 15 Number of infants dying during first 6 months of life



Analysis 02.16. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 16 Number of infants dying during first 12 months of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

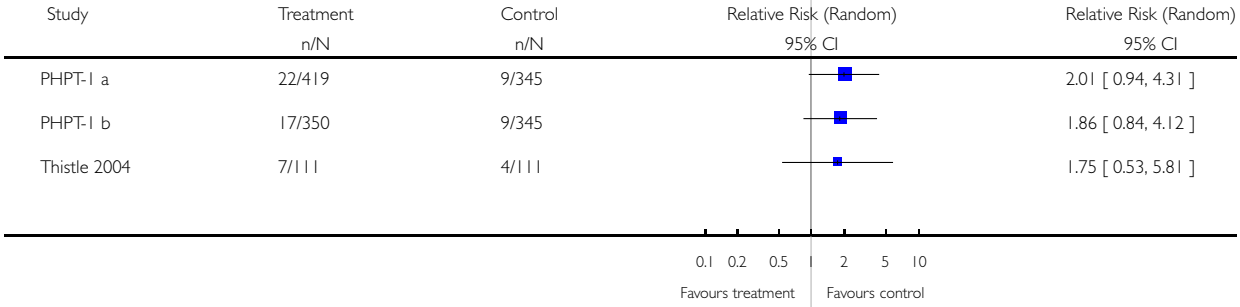
Outcome: 16 Number of infants dying during first 12 months of life

Analysis 02.19. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 19 Number of premature babies based on author's definition

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 19 Number of premature babies based on author's definition

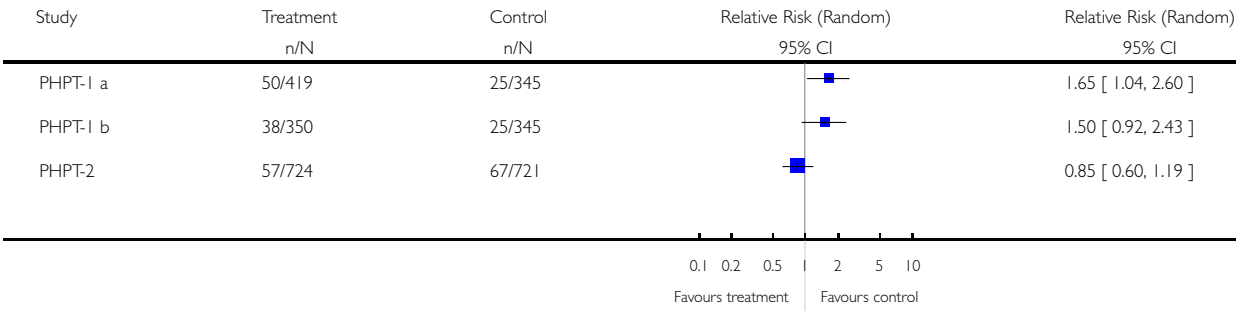


Analysis 02.20. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 20 Number of babies weighing less than 2.5kg.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 20 Number of babies weighing less than 2.5kg.

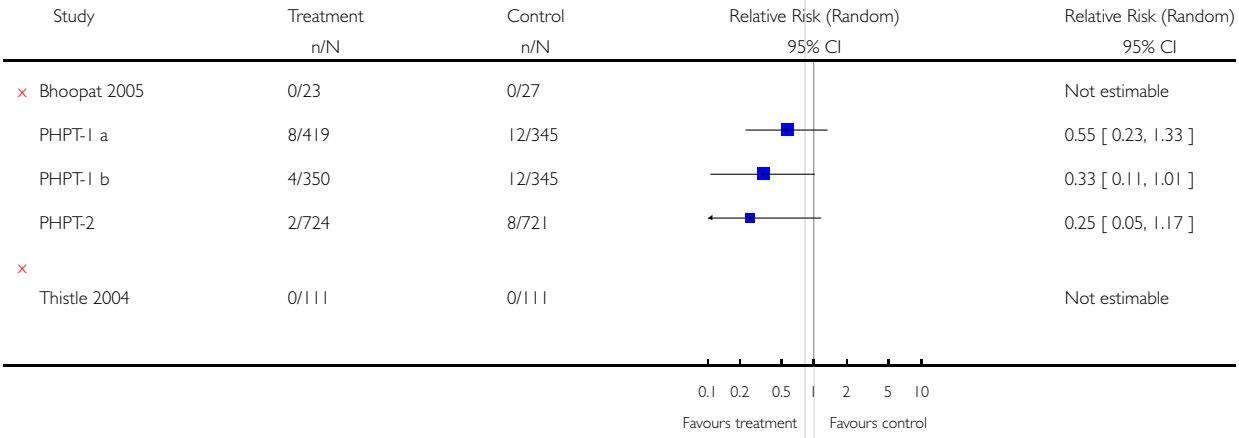


Analysis 02.21. Comparison 02 Longer versus shorter regimens using the same ARVs., Outcome 21 Stillbirth rates

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 02 Longer versus shorter regimens using the same ARVs.

Outcome: 21 Stillbirth rates



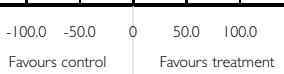
Analysis 03.01. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 01 HIV infection at birth

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 01 HIV infection at birth

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
Gray 2006 a	91	92	27.00 (76.00)		27.00 [-121.96, 175.96]
Gray 2006 b	94	92	53.00 (72.00)		53.00 [-88.12, 194.12]
Gray 2006 c	88	92	49.00 (74.00)		49.00 [-96.04, 194.04]
PACTG 316	631	637	2.00 (74.00)		2.00 [-143.04, 147.04]



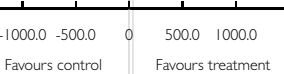
Analysis 03.02. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 02 HIV infection at 4 to 8 weeks.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 02 HIV infection at 4 to 8 weeks.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
HIVNET 012	310	370	41.00 (15.00)		41.00 [11.60, 70.40]
Taha 2003	444	421	37.00 (17.00)		37.00 [3.68, 70.32]
Taha 2004	444	445	13.00 (15.00)		13.00 [-16.40, 42.40]
02 Not breastfeeding					
Gray 2005	473	491	35.00 (23.00)		35.00 [-10.08, 80.08]
Gray 2006 a	91	92	-120.00 (92.00)		-120.00 [-300.32, 60.32]
Gray 2006 b	94	92	-42.00 (84.00)		-42.00 [-206.64, 122.64]
Gray 2006 c	88	92	24.00 (77.00)		24.00 [-126.92, 174.92]
Kiarie 2003	55	55	58.00 (32.00)		58.00 [-4.72, 120.72]
PACTG 316	631	637	13.00 (49.00)		13.00 [-83.04, 109.04]
SAINT	477	467	24.00 (15.00)		24.00 [-5.40, 53.40]



Analysis 03.03. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 03 HIV infection at 3 to 4 months.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 03 HIV infection at 3 to 4 months.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
HIVNET 012	310	370	39.00 (14.00)		39.00 [11.56, 66.44]
02 Not breastfeeding					
Gray 2005	473	491	40.00 (21.00)		40.00 [-1.16, 81.16]
Gray 2006 a	91	92	-145.00 (95.00)		-145.00 [-331.20, 41.20]
Gray 2006 b	94	92	-113.00 (91.00)		-113.00 [-291.36, 65.36]
Gray 2006 c	88	92	-1.00 (80.00)		-1.00 [-157.80, 155.80]

Analysis 03.04. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 04 HIV infection at 6 months

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 04 HIV infection at 6 months

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
02 Not breastfeeding					
Gray 2006 a	91	92	-116.00 (84.00)		-116.00 [-280.64, 48.64]
Gray 2006 b	94	92	-89.00 (81.00)		-89.00 [-247.76, 69.76]
Gray 2006 c	88	92	18.00 (70.00)		18.00 [-119.20, 155.20]

Analysis 03.05. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 05 HIV infection at 12 months

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 05 HIV infection at 12 months

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
HIVNET 012	310	370	36.00 (14.00)		36.00 [8.56, 63.44]

Analysis 03.06. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 06 HIV infection at 18 months

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 06 HIV infection at 18 months

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
HIVNET 012	310	370	39.00 (13.00)		39.00 [13.52, 64.48]

Analysis 03.07. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 07 HIV infection or death at 4 to 8 weeks.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 07 HIV infection or death at 4 to 8 weeks.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
HIVNET 012	310	370	42.00 (14.00)		42.00 [14.56, 69.44]

Analysis 03.08. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 08 HIV infection or death at 3 to 4 months.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 08 HIV infection or death at 3 to 4 months.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
HIVNET 012	310	370	40.00 (13.00)		40.00 [14.52, 65.48]

Analysis 03.10. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 10 HIV infection or death at 12 months.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 10 HIV infection or death at 12 months.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
HIVNET 012	310	370	32.00 (12.00)		32.00 [8.48, 55.52]

Analysis 03.11. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 11 HIV infection or death at 18 months.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 11 HIV infection or death at 18 months.

Study	Treatment N	Control N	efficacy (%) (SE)	efficacy (%) (Random) 95% CI	efficacy (%) (Random) 95% CI
01 Breastfeeding					
HIVNET 012	310	370	33.00 (12.00)		33.00 [9.48, 56.52]

Analysis 03.12. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 12 Number of infants dying during first 8 days of life.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 12 Number of infants dying during first 8 days of life.

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
HIVNET 012	5/313	2/313		2.50 [0.49, 12.79]

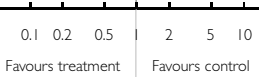
Analysis 03.13. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 13 Number of infants dying during first 4 to 8 weeks of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 13 Number of infants dying during first 4 to 8 weeks of life

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
Gray 2005	13/533	11/518		1.15 [0.52, 2.54]
HIVNET 012	10/313	4/313		2.50 [0.79, 7.89]
Kiarie 2003	3/70	3/69		0.99 [0.21, 4.72]
PACTG 316	3/754	5/752		0.60 [0.14, 2.50]
SAINT	19/657	19/662		1.01 [0.54, 1.89]
Taha 2003	15/557	12/562		1.26 [0.60, 2.67]
Taha 2004	7/448	4/446		1.74 [0.51, 5.91]



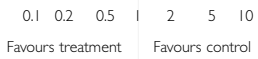
Analysis 03.15. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 15 Number of infants dying during first 6 moths of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 15 Number of infants dying during first 6 moths of life

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
Gray 2006 a	9/93	3/92		2.97 [0.83, 10.61]
Gray 2006 b	6/95	3/92		1.94 [0.50, 7.52]
Gray 2006 c	2/93	3/92		0.66 [0.11, 3.86]



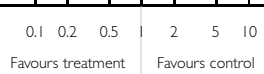
Analysis 03.17. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 17 Number of infants dying during first 18 months of life

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 17 Number of infants dying during first 18 months of life

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
HIVNET 012	42/313	34/313		1.24 [0.81, 1.89]



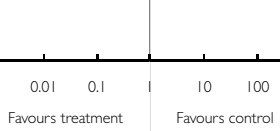
Analysis 03.19. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 19 Number of premature babies based on author's definition

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 19 Number of premature babies based on author's definition

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
Kiarie 2003	4/70	2/69		1.97 [0.37, 10.42]
PACTG 316	125/754	119/752		1.05 [0.83, 1.32]



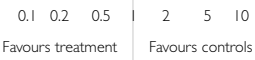
Analysis 03.20. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 20 Number of babies weighing less than 2.5kg, except SAINT: <2 kg.

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 20 Number of babies weighing less than 2.5kg, except SAINT: <2 kg.

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
HIVNET 012	14/313	21/313		0.67 [0.35, 1.29]
Kiarie 2003	2/70	1/69		1.97 [0.18, 21.24]
PACTG 316	86/754	75/752		1.14 [0.85, 1.53]
SAINT	7/657	5/662		1.41 [0.45, 4.42]



Analysis 03.21. Comparison 03 Regimens using different ARVs and durations of treatment., Outcome 21 Stillbirth rates

Review: Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

Comparison: 03 Regimens using different ARVs and durations of treatment.

Outcome: 21 Stillbirth rates

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
HIVNET 012	2/313	1/313		2.00 [0.18, 21.94]
Kiarie 2003	3/70	2/69		1.48 [0.25, 8.58]
PACTG 316	1/754	0/752		2.99 [0.12, 73.33]